Exhibit 20

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co., Ltd., Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai 5th Avenue, Linhai, Taizhou, Zhejiang 317016 China

FEI: **3003885745**

EI Start: 07/23/2018

EI End: 08/03/2018

TABLE OF CONTENTS

Min Li
ZHP-312
4/21/2021

RESTRICTED CONFIDENTIAL INFORMATION

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co., Ltd., Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai 5th Avenue, Linhai, Taizhou, Zhejiang 317016 China

FEI: **3003885745**

EI Start: 07/23/2018

EI End: 08/03/2018

SUMMARY

This foreign comprehensive For Cause inspection of an API (Active Pharmaceutical Ingredient) manufacturer was conducted in accordance of CPGM 7352.832 [redacted] Pre-Approval Inspections/Methods Validation, Drug Manufacturing Inspections, CPGM 7356.002F Active Pharmaceutical Ingredient Process Inspections, Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients ICH (International Conference on Harmonization Regulations) Q7, FY18 (Fiscal Year 2018) Foreign Drug Inspection assignment MARCS ID # 98345, and FACTS ID# 9501248 issued by IOG (Trip # 2018-318D) to determine compliance status. The inspection is reported under PAC (Program/Assignment Code) 52832. The inspection included coverage of profile class CSN (Non-sterile Active Pharmaceutical Ingredient by Chemical Synthesis).

The previous inspection dated May 2017 concluded with the issuance of a three item Form FDA 483, Inspectional Observations for:1) failure to investigate OOS/OOT, 2) failure to appropriately maintain equipment, and 3) OOS results invalidated without scientific justification. The previous inspection was initially classified OAI (Official Action Indicated) and reclassified VAI (Voluntary Action Indicated). Corrective actions were not adequate.

APIs covered include: Valsartan, Levetiracetam, and Tadalafil. The following systems were covered: Quality, Facilities and Equipment, Production, and Laboratory Control. Partial coverage was given to the Material System. The Packaging and Labeling System was not covered. Inspectional coverage for Tadalafil included verification of readiness for commercial manufacturing, conformance to [redacted], and data integrity audit. Batch production records, laboratory records, training records, logbooks, protocols, procedures, deviation investigations, change control, and stability study data were reviewed.

A Form FDA 483, Inspectional Observations, was issued at the close of the inspection for: 1) inadequate change control system; 2) inadequate validation program; 3) insufficient investigation of critical deviations; 4) the quality unit does not always fulfill the responsibilities of the quality unit; 5) cleaning procedures do not have sufficient detail; 6) equipment is not always of appropriate design; 7) preventive maintenance procedures are not always adequate; 8) lubricants, heating fluids and coolants are not always food grade lubricants and oils; 9) sampling plans are not always scientifically sound; 10) stability studies are not always adequate; and 11) production deviations are not always thoroughly investigated. There were no refusals. Samples were collected during this inspection, see the sample collection section of this report for details.

Management was warned failure to make corrections could result in regulatory action without further notification including but not limited to a warning letter or import detention. Management

RESTRICTED CONFIDENTIAL INFORMATION

did not agree with the observations. Management did not commit to making corrections. Mr. Jun Du, Executive Vice President, committed to submitting a written response to the U.S. Food and Drug Administration (FDA) within 15 business days.

ADMINISTRATIVE DATA

Inspected firm: Zhejiang Huahai Pharmaceutical Co., Ltd.
Location: Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai 5th Avenue
Linhai, Taizhou Zhejiang, 317016 China
Phone: +86 576 85016003
Mailing address: Coastal Industrial Zone, Chuannan No. 1 Branch No. 9
Donghai 5th Avenue
Linhai, Taizhou Zhejiang, 317016 China

Dates of inspection: 07/23/2018-07/28/2018, 07/30/2018-08/03/2018
Days in the facility: 11
Participants: Cheryl Clausen, Investigator and Joel Hustedt, Investigator

This inspection was supported by Lili Sang (during the period of 07/23/2018 – 07/28/2018), who is a Locally Engaged Staff (LES) hired by the United States Embassy in Beijing and assigned to FDA to work in support of FDA activities. All information, including documents collected during this inspection and any translation from local language to English by Lili Sang (LES) that supports the Form FDA 483, Inspectional Observations (if Form FDA 483 was issued) and the Establishment Inspection Report (EIR) was collected in collaboration with the FDA investigator(s).

On July 23, 2018 at Zhejiang Huahai Pharmaceutical Co., Ltd., Mr. Hustedt and I showed our credentials to Mr. Jun Du, Executive Vice President. Mr. Du stated he is the most responsible person at the facility. Mr. Jie Wang, Vice President Business Development Headquarters, provided an informational presentation. **Exhibit 132** is a list of those present for the opening meeting. On August 3, 2018, a Form FDA 484, Receipt for Samples, was issued to and signed by Mr. Du; and a Form FDA 483, Inspectional Observations, was issued to Mr. Du.

Post inspection correspondence should be addressed to: Mr. Jun Du, Executive Vice President, Zhejiang Huahai Pharmaceutical Co., Ltd., Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai 5th Avenue, Linhai, Taizhou Zhejiang 317016 China.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162351

Establishment Inspection Report

FEI: **3003885745**

Zhejiang Huahai Pharmaceutical Co., Ltd., Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai 5th Avenue, Linhai, Taizhou, Zhejiang 317016 China

EI Start: 07/23/2018

EI End: 08/03/2018

This was a team inspection consisting of Cheryl A. Clausen, Lead Investigator and Mr. Joel Hustedt, Investigator. Mr. Hustedt was present 07/23/2018-07/28/2018. This report was written by Investigator Clausen (CAC) with sections written by Mr. Hustedt (JDH).

Translation was provided by: Mr. Zi-Qiang Gu, Ph.D., Pharmaceutical Consultant (07/23/2018 – 07/26/2018); and Mr. Wayne Cheng, Deputy QA Manager (07/26/2018, 07/30/2018 – 08/03/2018).

Representatives from the local government present during this inspection and dates present include: Mr. Xu Dan, Division of Drug and Cosmetic Inspection, Inspector (07/23/2018-07/27/2018); Ms. Chen Liu, Zhejiang Center for Drug Certification & Inspection, Technical Officer (07/23/2018-07/27/2018); Mr. Peng Wang, Safety Supervisor Department of Taizhou Market Supervision Administration, Deputy Director (07/23/2018-07/28/2018, 07/30/2018-08/03/2018); Ms. Bo JU, Zhejiang FDA, Commissioner (07/28/2018, 07/30/2018-08/03/2018); Mr. Weidong Wang, Zhejiang Center for Drug Inspection, Supervisor (08/03/2018); Mr. Xingfu YE, Taizhou Market Supervision Administration, Deputy Director General (08/03/2018); and Mr. Hailel Chen, Safety Supervision Department of Taizhou Market Supervision Administration, Director (08/03/2018).

HISTORY

Zhejiang Huahai Pharmaceutical Co., Ltd. is a limited liability company established in 1989. Corporate headquarters are located at: Zhejiang Pharmaceutical Co., Ltd. Xunqiao, Linhai, Zhejiang 317024 China (FEI: 3003999190). Manufacturing operations occur at headquarters and this site. Subsidiary Zhejiang Pharmaceutical Co., Ltd. Duchuan Road, Duqiao, Linhai, Zhejiang 317016 China manufacture intermediates only. Zhejiang Huahai Pharmaceutical Co., Ltd. does not have a history of regulatory action. The firm is currently the subject of a recall for Valsartan initiated shortly before the start of this inspection. Please refer to the Recall section of this report for further information.

The firm operates 7 days a week 24 hours a day. Business offices are open 8:00 AM – 5:30 PM. Plant shifts are 7:30 AM – 3:30 PM, 3:30 PM – 11:30 PM, and 11:30 PM – 7:30 AM. The firm does not have planned periods for extended shutdown. The firm has 2,042 full time employees including 1,338 involved in manufacturing operations, 185 involved in quality operations, and 519 involved in other activities.

The firm's drug registration is current for 2018. **Exhibit 136** includes an aerial view of the site layout.

RESTRICTED CONFIDENTIAL INFORMATION

INTERSTATE COMMERCE

Zhejiang Huahai Pharmaceutical Co., Ltd. commercially manufactures APIs intended for use in the manufacture of finished dosage drug products shipped to the U.S. The firm transports finished APIs by truck and then air to foreign finished dosage drug manufacturers who then ship finished dosage drug products to the U.S. **Exhibit 137** is a list of consignees manufacturing finished dosage drug products for shipment to the U.S.

Valsartan batches C5355-18-009M, C5355-18-010M, C5355-18-011M, and C5355-18-012M were shipped to fulfill Purchase Order (PO) 4500653172 placed February 1, 2018 [**Exhibit 140 page 1**]. Packing List for Invoice No. HH2018329 includes Valsartan batches C5355-18-009M, C5355-18-010M, C5355-18-011M, and C5355-18-012M date February 5, 2018 [**Exhibit 141 page 6**]. Airwaybill FGSAE18020011 for PO number 4500653172 placed February 1, 2018 shows the shipment was received February 7, 2018 at Sunoble International Cargo Services Inc. in Shanghai, China for shipment to Novartis Pharma Stein AG located at Schaffhauserstrasse 101, Werk Stein Bau 190 4332 Stein, Switzerland [**Exhibit 140 page 7**]. Zhejiang Huahai Pharmaceutical Co., Ltd. Commercial Invoice No. HH2018329 was issued February 5, 2018, for PO number 4500653172 [**Exhibit 140 page 8**].

Exhibit 187 lists the batch numbers for Valsartan batches shipped to consignee Torrent Pharmaceuticals Ltd. located in Ahmedabad, India.

JURISDICTION

Zhejiang Huahai Pharmaceutical Co., Ltd. manufactures APIs subject to portions of the Food, Drug, and Cosmetic Act. **Exhibit 138** is a list of products manufactured at this site. **Exhibit 139** lists Valsartan shipments 2016-2018 shipped to finished dosage manufacturers intended for further manufacture and shipment to the U.S. **Exhibit 141** includes labels and labeling for Valsartan batch C5355-18-009M.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

Mr. Jun Du, Executive Vice President - Mr. Du is overall responsible for site operations including correcting cGMP deficiencies. **Exhibit 133** is a job description for Mr. Du. Mr. Du reports to Mr. Bauhua Chen, President, located at Zhejiang Huahai Pharmaceutical Co., Ltd. headquarters in Xunqiao. Mr. Du was present for the opening meeting, daily wrap-up discussions, and the close out meeting.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162353

Ms. Jucai GE, QA Director - Ms. GE is responsible for all quality assurance functions including preventing GMP violations. **Exhibit 134** is a job description for Ms. GE. Ms. GE reports to Mr. Jenson YE, QA Vice President Headquarters. Ms. GE was present throughout the inspection, answered questions, provided documents, and was present for the opening meeting, daily wrap-up discussions, and the close out meeting.

Various other individuals assisted and were interviewed throughout the inspection. **Exhibit 135** is a list of Directors as of July 24, 2018. **Exhibit 136** includes an organizational chart. The firm's U.S. Agent is: Mr. Xiaodi Guo, PhD., Executive Vice President, HuaHai U.S. Inc., Cranbury, New Jersey 08512; phone 609-655-1688, email xguo@huahaipharmus.com.

FIRM'S TRAINING PROGRAM

The firm has a written training procedure requiring at least annual GMP training. Training is evaluated through written examination. Trainees are required to answer at least 75% of the questions correctly. Employees scoring below 75% are retrained. I reviewed training records for: Shelei Feng, QC Analyst; Weifeng Yang, Production Operator; and Chenglong Shan, Maintenance. Nothing remarkable was noted.

MANUFACTURING OPERATIONS

The firm does not use any new or unusual components, raw materials, or equipment. The manufacturing process for Valsartan, USP consists of dispensing, distillation, condensation, filtration, crystallization, centrifugation, drying, milling, and packaging. Manufacturing suites and equipment used in the manufacture of Valsartan, USP are dedicated. **Exhibit 143** is list of dedicated equipment used in the manufacture of Valsartan in each Workshop. Manufacturing suites and equipment used in the manufacture of Tadalafil are not dedicated. **Exhibit 142** is the equipment list for non-dedicated Workshop 5 with the APIs manufactured using each piece of equipment.

Mr. Jun Du, Executive Vice President, stated Novartis placed an order for 45 Metric tons of Valsartan early in 2018. **Exhibit 145** is the POs (Purchase Order) from Novartis for fulfillment of the order. **Exhibit 144** is the Invoices the firm issued for the POs from Novartis.

QUALITY

Zhejiang Huahai Pharmaceutical Co., Ltd. has an established Quality Unit consisting of the Quality Assurance department and the Quality Control laboratories. The firm has established written procedures for the quality unit covering supplier qualification, training, batch release, validation,

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162354

calibration, investigations including deviations and Out-of-Specification (OOS); product recall, stability studies and complaints. Throughout the inspection, I observed employee practices, reviewed documents, and conducted personal interviews with various staff members to assess whether the firm's quality system is designed to achieve sufficient control over the facility and commercial manufacturing operations. Through these activities, I observed the Quality Unit is involved in activities including but not limited to: review of manufacturing documents and approval of product prior to release; qualification and validation activities; deviations and investigations; and change control activities.

The firm has a written procedure for Annual Product Quality Review (APQR) Management System SMP-020.06 effective November 15, 2017 [**Exhibit 173**]. The firm's APQR procedure is silent regarding conducting year-to-year trending to identify potential shifts in the manufacturing process. I reviewed the APQR for Valsartan Workshop 2 East C5355 December 25, 2015 to December 24, 2016. The firm does not conduct year-to-year trending to identify potential shifts in the manufacturing process.

The quality unit does not always fulfill the responsibilities of the quality unit to release or reject all APIs (**FDA Observation 4**). The quality unit does not always demonstrate the firm has the written procedures necessary to conduct deviation investigations and/or the firm's quality unit has the authority and responsibility to ensure all critical deviations are thoroughly investigated (**FDA Observation 3a, 3bi, 3bii, 3biii,3c, 3d, and 3e**). The firm does not have an adequate change control system to evaluate changes that may impact intermediates and APIs (**FDA 483 Observation 1ai, 1aii, 1bi, 1bii, 1c, and 1d**). Risk assessments are not always thorough or documented. The firm initiates commercial scale changes based on lab scale research projects.

Ongoing deviation investigation for Deviation Number DCE-18001 was initiated June 6, 2018, for a suspected genotoxic impurity in Valsartan [**Exhibit 113**]. The firm's customer (Novartis) informed the firm the customer identified a small unknown peak after the Toluene peak during residual solvent testing using a GC-FID instrument that led the customer to send samples to a third-party laboratory for identification of the unknown peak (the third-party laboratory identified the unknown peak as NDMA (N-Nitrosodimethylamine)) [**Exhibit 113 page 1 Section Description**]. The Deviation Report for Deviation Number DCE-18001 prepared July 20, 2018, states the presence of trace amounts of NDMA in the final Valsartan API requires the convergence of the following three factors: i) use of dimethylformamide in the tetrazole formation step, ii) quenching of azide using nitrous acid, and iii) quenching takes place in the presence of the product [**Exhibit 113 page 20**]. I asked Mr. Min Li, Ph.D. (Bio-organic and Analytical Chemistry), Vice President Analytical Operations Headquarters, if the firm recreated the circumstances of the firm's hypothesis and then conducted tests to verify the firm's hypothesis regarding the formation of NDMA in Valsartan API. Dr. Li stated it was not necessary to do that because based on the firm's knowledge and experience everyone retrospectively agrees this is the cause and the firm conducted a lab scale test for Valsartan

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162355

API produced separate from the quenching step and did not find NDMA in the Valsartan API produced from a separate quenching step. Dr. Li stated the firm would recreate the circumstances stated in the firm's hypothesis to verify the hypothesis. No information was provided before the close of this inspection regarding the outcome of the firm's test to confirm the firm's hypothesis.

I asked Dr. Li if the firm tested the firm's other sartan type finished APIs for NDMA. Dr. Li stated the firm tested other sartan type finished APIs manufactured by the firm and did not find NDMA. Dr. Li stated the firm did a reverse study where the firm separated the intermediate Valsartan crude from the quenching step on a lab scale and no NDMA formed.

I asked Dr. Li if the firm evaluated the contribution of batch size and the impact of batch size on the variation in the concentration of NDMA between the different workshops. Dr. Li stated the firm has not looked at this. Dr. Li stated the firm will look into this to evaluate the impact.

In Deviation Report for Deviation Number DCE-18001, the firm states NDMA will not be generated in Valsartan batches manufactured using Process I or Process II (Triethylamine(TEA)), since no DMF is used [**Exhibit 113 page 43**]. On August 1, 2018, I asked Mr. Du if the firm tested Valsartan API manufactured for the Chinese market using Process II (TEA) manufacturing process for NDMA and if so, the results of those tests. On August 2, 2018, Mr. Du stated the firm tested Valsartan API manufactured for the Chinese market using Process II (TEA) manufacturing process and found from 11 ppm to 107 ppm NDMA in the batches tested. I asked Mr. Du if the firm planned to re-evaluate the firm's hypothesis or if the firm planned to continue the current process validation to separate the Valsartan intermediate product from the quenching step in chemical synthesis step 4. Mr. Du stated the firm plans to continue the current process validation to separate the Valsartan intermediate product from the quenching step in chemical synthesis step 4. **Exhibit 114** shows a comparison of Valsartan Triethylamine Hydrochloride Process Parameters manufactured for the US market and the Chinese market.

Dr. Li stated it is not scientifically possible to remove NDMA by recrystallization. In Deviation Report for Deviation Number DCE-18001, the firm states all returned and quarantined Valsartan API batches will be reprocessed and tested against revised specification (< 0.3 ppm NDMA) [**Exhibit 113 page 45**]. DMF# 23491 Valsartan, USP (Process II) includes one option for reprocessing the drug substance, recrystallization [**Exhibit 115**].

From January 2016 to July 2018 the firm rejected a total of 15 batches of APIs and received a total of 7 batches of APIs manufactured for the US market [**Exhibit 186**]. I asked Ms. GE if the firm reprocessed all rejected and returned APIs. Ms. GE stated yes. I asked Ms. GE if the firm conducts additional impurity testing on rejected and returned batches. Ms. GE stated no. I asked Ms. GE if the firm evaluated the potential risk of introducing unknown impurities into the firm's

manufacturing Workshops from reprocessing rejected and returned batches. Ms. GE stated the finished APIs meet product release testing specifications.

The firm has a written procedure Reprocess and Rework Management Procedure SMP-025.3 effective January 30, 2018 [**Exhibit 171**]. **Exhibit 171 page 7 section 5.5** specifies an "R" or a "W" is added to the batch number so the batch number can be traced to the original batch. However, the final API batch number after reprocessing does not indicate the batch was reprocessed. I asked Ms. Yuelin Hu, Assistant Director QA, if the final API batch number indicates whether a batch has been reprocessed. Ms. Hu stated no. **Exhibit 171 page 7 section 5.7.2** specifies a risk assessment is used to determine whether the reprocessed batch is added to the firm's stability study program. Ms. GE stated the first reprocessed batch is added to the firm's stability study program. I asked Ms. GE if she meant only the first reprocessed batch is added to the firm's stability study program. Ms. GE responded yes.

I reviewed the Stability Protocol for Valsartan, USP CS-12-005 implementation date January 11, 2012. All data reported was within specification. Results were similar across U.S. and non-U.S. markets.

Validation of production processes, cleaning procedures, and analytical methods is not always adequate (**FDA 483 Observation 2a, 2bi, 2bii, 2bii, 2c, 2d, and 2e**). Valsartan Impurities Profile Analysis Report-01 written April 10, 2012 [**Exhibit 176**] is an example of the firm's process for evaluating impurities in final APIs. Due to time constraints, I did not review the impurity profile for all APIs intended for manufacture of finished dosage drug products shipped to the U.S. I asked Ms. GE if the impurity profile for Valsartan would be representative of the impurity profiles for all final APIs manufactured at the firm. Ms. GE stated yes.

I asked Mr. Peng Dong, Deputy Director East Zone, if the firm added controls to minimize NDMA in Valsartan for: raw materials, intermediates, and/or solvents; equipment operating conditions; IPC (In-process Control) testing; stability studies; hold times; or storage conditions. Mr. Dong stated no. Mr. Dong stated the firm's optimized process will eliminate NDMA in Valsartan so there is no need for additional controls. I asked Mr. Dong if the firm has data comparing the concentration of NDMA in reprocessed Valsartan batches and Valsartan batches that have not been reprocessed. Mr. Dong stated no.

Process Validation Protocol Zinc Chloride Process of Valsartan Workshop II CNVP-11-075 includes a specification for Valsartan intermediate crude Related Substance by HPLC for impurity peak, Pentacylated Deformylation Compound at RRT 1.7 $\leq$ 1.0% [**Exhibit 102**]. The final Valsartan API does not have a specification for Related Substance by HPLC at RRT 1.7 $\leq$ 1.0%. I asked Mr. Dong if the same Related Substance by HPLC test method is used to test both the intermediate crude

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162357

Valsartan and the final Valsartan API. Mr. Dong stated yes. I asked Mr. Dong why the final Valsartan API does not include a specification for Related Substance by HPLC at RRT 1.7 ≤ 1.0%. Mr. Dong stated in the final Valsartan API this impurity peak is controlled in the single unspecified impurity (specification ≤ 1.0%). I asked Mr. Dong how long the firm has been aware of an impurity at RRT 1.7 ≤ 1.0%. Mr. Dong stated the firm has been aware of an impurity at RRT 1.7 since the manufacturing process for Valsartan was first developed in-house in 2008. I asked Mr. Dong for the concentration range of impurity peak at RRT 1.7 in intermediate crude Valsartan for the TEA process and the DMF process. Mr. Dong stated the concentration range for this impurity peak for the TEA process is 0.2% to 0.6% and < 0.2% for the DMF process.

PRE-APPROVAL [redacted]

The firm's readiness for commercial manufacturing of the API in the following [redacted] was assessed: [redacted]. Zhejiang Huahai Pharmaceutical Co., Ltd. is listed in the [redacted] as the manufacturer of Valsartan, USP API. The three primary inspectional objectives of the preapproval inspection program were covered during this inspection.

OBJECTIVE 1: READINESS FOR COMMERCIAL MANUFACTURING

I reviewed the firm's written procedures and protocols for batch release, change control, deviations, complaints, sampling, testing, qualification, validation, and the drug development report. Tadalafil Impurity Profile Analysis Report indicates the firm will test the first three batches each year for genotoxic impurity Methyl Chloroacetate and the firm will not include testing of Methyl Chloroacetate in product release testing. I asked Mr. Dong if the final Tadalafil API release testing will include testing for genotoxic impurity Methyl Chloroacetate. Mr. Dong stated no.

The firm does not have adequate systems in place for change control, investigation of deviations, sampling or validation (**FDA 483 Observations 1, 2, 3, 9**). Cleaning procedures do not include sufficient detail to ensure equipment is cleaned in a reproducible and consistent manner (**FDA 483 Observation 5**). The firm does not take and test rinse samples from each reactor. The firm takes one rinse sample at the end of the equipment train and tests the rinse sample for TOC (Total Organic Carbon). The firm does not test rinse and/or swab samples for product residue, product degradants, solvent residue, or solvent degradants. I asked Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, if the firm tests rinse and/or swab samples for product residue, product degradants, solvent residue, or solvent degradants. Mr. Q. Li stated no the firm tests for TOC because a TOC test gives the firm information regarding the presence of any organic carbons. I asked Mr. Q. Li if the firm has data showing TOC testing can identify specific impurities and/or degradants. Mr. Q. Li stated no.

RESTRICTED CONFIDENTIAL INFORMATION

The firm does not ensure coolants are food grade (**FDA 483 Observation 8**). Equipment is not always adequate for intended use (**FDA 483 Observation 6b and 6c**). The firm's stability study program is not adequate (**FDA 483 Observation 10**).

The firm commercially manufactures Tadalafil for non-US markets in Workshop W05. I verified proposed commercial processes and manufacturing batch records. I reviewed an executed batch record. During packaging the firm passes the final API through a ferrous metal detector. I asked Ms. GE why the firm does not use both a ferrous and non-ferrous metal detector. Ms. GE stated if a non-ferrous metal is present the firm will see the anomaly. I asked Ms. GE how the firm will detect sub-visible non-ferrous metal particles. Ms. GE understood the question, she acknowledged the question, but she did not provide a verbal response. I reviewed the firm's written procedure for vendor qualification and vendor qualification forms. I observed employee practices, reviewed documents, and conducted personal interviews with various staff members to evaluate the effectiveness of the firm's quality system and the ability of quality to control the facility and commercial operations.

OBJECTIVE 2: CONFORMANCE TO [redacted]

I conducted personal interviews with various staff members to assess whether the firm's proposed commercial manufacturing operations are consistent with the [redacted] The proposed commercial scale is the same size as the exhibit batches submitted in the [redacted] I verified the formulation is consistent with the [redacted] I reviewed the product development report for Tadalafil. Nothing remarkable was noted.

OBJECTIVE 3: DATA INTEGRITY AUDIT

I observed employee practices, instrument calibration and usage logbooks, electronic records and conducted personal interviews with various staff members to verify the firm's current practices. I verified the firm has the necessary instruments to conduct required testing for the approval and release of the finished product. Laboratory instruments are qualified and calibrated. I reviewed raw data submitted as part of the firm's drug [redacted] for product release testing and stability study testing. Nothing remarkable was noted.

FACILITIES AND EQUIPMENT

The manufacturing facility is a non-dedicated manufacturing facility. No highly sensitizing, cephalosporins, teratogens, cytotoxic materials, beta-lactams, non-penicillin beta-lactams, steroids, hormones, pesticides, or other non-pharmaceutical chemicals are manufactured at this facility. The

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162359

firm has specifically designed areas for manufacturing operations. No deficiencies were noted regarding lighting, potable water, toilet facilities, sewage and refuse disposal; or the use of other rodenticides, fungicides, insecticides, cleaning and sanitizing agents.

The firm has written facility cleaning and maintenance procedures. The firm has an on-going preventive maintenance program. The firm regularly cleans the facility.

The facility layout is designed to control the flow of people and materials through the manufacturing area. General air handling systems are in place. Pressure differentials between the corridor and manufacturing suites are designed to prevent cross-contamination.

EQUIPMENT

Equipment used in the manufacture of Valsartan, USP includes but is not limited to: reactors, centrifuges, filter presses, and a double cone rotary dryer. Equipment is assigned a unique equipment identification number. No deficiencies were noted regarding equipment size or location.

The firm does not use food grade coolants in jacketed reactors used in the firm's workshops (**FDA Observation 8**). The firm does not have validated cleaning procedures (**FDA 483 Observation 2e**). Cleaning procedures do not contain sufficient details to ensure cleaning procedures are consistently followed (**FDA 483 Observation 5**). Equipment is not always appropriately designed for its intended use, cleaning, and maintenance (**FDA Observation 6a, 6b, and 6c**). Preventive maintenance schedules are not always adequate (**FDA483 Observation 7a, 7b, and 7c**).

MATERIALS MANAGEMENT

Components, containers and closures are identified. Incoming components, containers and closures are quarantined until sampled, tested, approved and released for use. At least one specific identity test is conducted for each component. Containers and closures are visually examined. Components, containers and closures are used on a FIFO (First-in-First-out) basis. Partial coverage was given to the Materials Management System.

Sampling procedures do not always ensure samples are representative (**FDA 483 Observation 9**). The firm has a written procedure for vendor qualification Management System of API Material Supplier SMP-015.08 effective October 1, 2017. Management System of API Material Supplier is silent regarding the allowable difference in results between the manufacturer's CoA (Certificate of Analysis) reported test results and the firm's test results as part of verification of the reliability of the manufacturer's CoA. I reviewed the firms audit report for the manufacture of starting material, Br-OTBN. Nothing remarkable was noted.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162360

PRODUCTION

No deficiencies were noted regarding charging in of components, manufacturing formulation, identification of equipment with contents, calculation and documentation of yield, and equipment cleaning and use logs. The firm started manufacturing Valsartan, USP for validation of the firm's new optimized process for Valsartan July 23, 2018. Manufacturing of the first Valsartan batch was not completed prior to the end of this inspection. The firm did not have an approved validation protocol prior to July 23, 2018.

The firm's change control system to evaluate changes that may affect the production and control of intermediates or APIs is not adequate (**FDA 483 Observation 1ai, 1aii, 1bi, and 1bii**). Validation of manufacturing processes is not always adequate (**FDA Observation 2a, 2bi, 2bii, 2biii, 2c and 2d**). Production deviations are not always adequately reported and evaluated and critical deviations are not always investigated (**FDA 483 Observation 11a and 11b**).

The firm has a written procedure Deviation Investigation Management System SMP-017.05 effective January 1, 2018. Deviation investigations are not always thoroughly investigated and documented [**Exhibit 121**] (**FDA Observation 3c**). On-going deviation investigation DCE-18001 was initiated June 6, 2018 [**Exhibit 113**]. The deviation investigation was initiated for suspected genotoxic impurity in Valsartan. On June 6, 2018 Novartis notified the firm test results from a third-party laboratory found a small peak after the Toluene peak during Residual Solvent testing using a GC-MS test method. Dr. Li stated retrospectively the firm knew a very tiny peak (like noise) would elute after Toluene in GC-FID testing. Novartis notified the firm Novartis suspected the peak was NDMA (N-Nitrosodimethylamine). **Exhibit 165** includes chromatographs from GC-FID testing from three batches manufactured using Process II (TEA) manufacturing process prior to changing to Process II (DMF) and three batches manufactured as part of process validation for the new process. The peak location and peak size is consistent both before the change and after the change. **Exhibit 177** is the CoAs (Certificates of Analysis) for the six Valsartan batches manufactured before and after the change.

Mr. Du stated Novartis has the largest market share in China. Mr. Du stated Valsartan API manufactured using Process II (TEA) was approved for sale in China in June 2012. Mr. Du stated finished dosage Valsartan was approved for sale in China May 23, 2018 [**Exhibit 163**]. Valsartan API manufactured using Process II (DMF) was approved for sale in China in May 2017 [**Exhibit 113 page 21**].

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162361

DCE-18001 is classified as a major deviation. As part of the deviation investigation the firm prepared a Deviation Investigation Report dated July 20, 2018 [**Exhibit 113 pages 12-120**]. On June 9, 2018, the firm used a qualitative GC-MS method to confirm the structure of the unknown peak is NDMA. The firm is in the process of developing a validated quantitative GC-MS method for testing NDMA concentrations [**Exhibit 164**]. The firm hypothesizes the presence of trace amounts of NDMA in the final Valsartan API requires the convergence of the following three factors: 1) use of DMF in the tetrazole formation step, 2) quenching of azide using nitrous acid, and 3) quenching takes place in the presence of the product [**Exhibit 113 page 20**].

The firm has had three different manufacturing processes for the manufacture of Valsartan. Mr. Du stated Process I was never commercialized. Valsartan manufactured from Process II [(TEA) Triethylamine Hydrochloride catalyst and Toluene solvent)] was assigned the following product codes: C5069, C5354, and D5195. Valsartan manufactured from Process II [(DMF) Dimethyl Formamide solvent and Zinc Chloride catalyst] was assigned the following product codes: C5355 (manufactured in Workshop 2), C5523 (manufactured in Workshop 13) and D5191 (manufactured in Workshop W02). Product codes containing the letter "D" indicate the product is manufactured in a workshop in the West Zone. Product codes containing the letter "C" indicate the product is manufactured in a workshop in the East Zone.

The firm tested three Valsartan batches manufactured using Process II (TEA): C5354-11-001, C5354-11-002, and C5354-11-003 using an un-validated GC-MS method and detected no NDMA (LOQ about 1 ppm). The firm hypothesizes other sartan drugs will not have NDMA because the three factors that must converge do not exist in other sartan drugs manufactured at the firm. The firm tested three lots from 6 of the 7 sartan APIs the firm manufactures and did not detect NDMA [**Exhibit 113 page 34**].

On August 1, 2018, I asked Mr. Du if the firm tested Valsartan manufactured using Process II (TEA) processing method for the Chinese market for NDMA. On August 2, 2018, Mr. Du stated the firm tested Valsartan manufactured using Process II (TEA) processing method for the Chinese market for NDMA on July 8, 2018 and obtained results for NDMA ranging from 11 ppm – 107 ppm with an average NDMA concentration of 56 ppm. I asked Mr. Du for a second time if the firm intended to re-evaluate the firm's plan to continue with process validation for the optimized process now that NDMA was identified in Valsartan manufactured using Process II (TEA). Mr. Du stated no the firm intends to move forward with the new optimized process.

In the Deviation Investigation Report prepared July 20, 2018, the firm states the firm has developed and validated a sensitive GC-MS method that is suitable for testing the amounts of NDMA present in Valsartan batches [**Exhibit 113 page 43**]. On July 24, 2018, I asked for a copy of the firm's GC-MS test method for testing NDMA [**Exhibit 165**]. Dr. Li stated the test method is not yet approved. The Deviation Investigation Report reports GC-MS test method validation completed July 31, 2018 (11 days after the report was prepared) [**Exhibit 113 page 44**]. Dr. Li stated the GC-MS headspace test

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162362

method was developed by the firm's on-site R&D (Research and Development) Laboratory. Dr. Li stated the Butyl-acetate impurity in Ethyl Acetate interferes with the ability to quantify NDMA. Dr. Li also stated if the Butyl-acetate co-elutes it gives a false positive.

I asked Dr. Li if the firm developed reaction equations for the potential side reactions as part of the firm's drug development for the new optimized process. Dr. Li stated no it isn't necessary. I asked Dr. Li if the firm will test for potential side reaction products and impurities and test the waste streams for potential side reaction products and impurities. Dr. Li stated no it isn't necessary.

The firm has master production batch records. Valsartan is manufactured in four different Workshops. There is a separate approved master production record for each Workshop. Mr. Dong stated if changes to the DMF (Drug Master File) require revision to the master production batch records the batch records are revised. I asked Mr. Dong if the DMF number is included in the master batch record. Mr. Dong stated no. I asked Mr. Dong how the firm can tell version of the DMF a master batch record is revised for. Mr. Dong stated he thought you could tell by the date a master batch record is approved. **Exhibit 168** lists the batch record version number for each Workshop associated with each DMF amendment. **Exhibit 169** lists the solvent used for each version of the DMF. **Exhibit 170** lists the solvent used in each Workshop.

I asked Ms. GE how the firm ensures the correct version of the batch record is issued for use. Ms. GE stated when the DMF is approved through approval of the customer's NDA (New Drug Application) the firm initiates change control to revise the master batch record. Ms. GE stated the revised batch record has a new version number.

(JDH) The firm has manufactured Valsartan in five workshops since 2008 using the processes referred to as the "triethylamine process" and "zinc chloride process". **Exhibit 41** lists the history of changes to the firm's Valsartan DMF 23491. As part of technical amendment 004, submitted in December 2013, the firm changed the manufacturing process which included changing the catalyst reagent to zinc chloride in step 4 (synthesis of crude valsartan) and adding solvents DMF (Dimethyl Formamide) and MTBE (Methyl Tert-butyl Ether) in steps 3 and 4. **Exhibit 29** includes a general comparison of solvents used in the earlier "triethylamine process" and the DMF/zinc chloride process.

There are five major steps in the manufacture of Valsartan:

Step 1 – Synthesis of L-valine methyl ester hydrochloride
Step 2 – Synthesis of N-[(2-cyano-biphenyl-4-yl)-methyl]-L-methyl valinate hydrochloride
Step 3 – Synthesis of N-pentanoyl-N-[2'-cyano-biphenyl-4-yl)-methyl]-L-methyl valinate
Step 4 – Synthesis of crude Valsartan
Step 5 – Recrystallization

The manufacture of crude Valsartan (Step 4) in workshops 2, 13, and W02 was the focus of this inspection as they are currently used for manufacturing USDMF-specification Valsartan, which is intended for the U.S. market. I conducted walkthrough inspections of the crude Valsartan manufacturing areas in workshops 2, 13, and W02.

Workshop 4 has not been used since 2015 and workshop 12 was undergoing a complete renovation at the time of this inspection. All synthesis equipment had been removed from the facility and equipment throughout the clean area was being disassembled. The work began in June and is expected to be completed in the coming months. A change control describing the renovations to workshop 12 is included in **Exhibit 38.** The stated purpose of the change on the first page of the document translates as "To better satisfy the EHS (Environment, Health, Safety) requirement, to improve the operating environment of the workshop, to maintain and repair equipment, facilities, and workshop, to make the layout more rational."

A general process flow for the currently filed manufacturing process (zinc chloride process) for Valsartan in workshop 2, as an example, is included in **Exhibit 28. Exhibit 31** is a flow chart for the "optimized" process that will separate the quenching process believed to be a contributing factor to the formation of the NDMA impurity. This process is currently being validated by the firm. The first finished batches using this optimized manufacturing process were nearing completion at the time of the inspection. **Exhibit 39** shows the master batch record for the optimized crude Valsartan manufacturing process in workshop 2**. Exhibit 40** is a translated copy of this batch record**.**

The firm's evaluation and determination of the source of the formation of NDMA is explained in Deviation CDZ-18001 [**Exhibit 30, page 32**]. **Exhibit 46** provides details for specific manufacturing process steps in each of the workshops used to manufacture crude Valsartan with a summary of the firm's test results for the presence of NDMA for each workshop. Due to differences in the workshops the step numbers are slightly different from workshop to workshop. **Exhibits 32-34** include the crude Valsartan (step 4) batch records for the DMF/zinc chloride process in workshops 2, 13, and W02. **Exhibits 35-37** include English translations for each batch record.

LABORATORY/DESIGN OPERATIONS

Throughout the inspection, I interviewed employees and reviewed documentation associated with laboratory activities. Laboratory equipment includes but is not limited to: HPLCs, GCs, and UV-Vis Spectrophotometers. No deficiencies were noted regarding staffing, laboratory facilities, calibration, system suitability checks, or official standards. Sampling procedures are not always scientifically sound and/or they do not contain sufficient detail to ensure samples collected are representative (**FDA 483 Observation 9a, 9bi, 9bii, and 9c**).

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162364

The firm has a written procedure Recording and Reviewing for Laboratory Records QC-021.11 effective January 31, 2018. Data is reviewed by a second analyst in the laboratory who also conducts tests. Data is reviewed prior to batch release. Data is also reviewed again monthly. Prior to batch release data review includes a review of: audit trails, integration, repeated integration, manual integration, repeated sequence, and single injections.

The firm continues the practice of making additional injections for Assay results which are not within 2% of each other as shown in the injection history for HPLC injections [**Exhibit 185**]. I asked Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, why the firm is making repeat injections for Assay results within specification. Mr. Q. Li stated the Assay results are not very accurate and the firm wants to report the most accurate result. I asked Mr. Q. Li if the firm calculated the level of accuracy of the test method. Mr. Q. Li stated no. I asked Mr. Q. Li if the firm needed to develop and validate a new method given repeat injections can't improve the accuracy of the results or improve the accuracy of the test method. Mr. Q. Li understood my question, acknowledged my question, but did not provide a verbal response.

The manufacturing process for Valsartan is the same since December 2017 for all markets. **Exhibit 161** compares the product release specifications for Valsartan for each market. In-house test methods are used for Related Substances, Residual Solvents and Assay test methods.

The firm does not have an adequate procedure(s) for responding to and handling the identification of unknown peaks. The firm's written procedure API Chromatographic System Suitability Integrity Evaluation QC-013-6 effective September 20, 2017 states if abnormal peak report to QC Supervisor or Team Leader [**Exhibit 184 page 6 section 5.1.5.1.3**]. Mr. Yinhua Tang, Assistant Director QC, stated new peaks, ghost peaks, abnormal peaks, unspecified impurity peaks are only investigated if the peak is OOT (Out-of-Trend). I asked Mr. Tang if the firm has another written procedure(s) providing more details for how to handle any type abnormal, unknown, or unidentified peak. Mr. Tang stated no. I reviewed six OOS investigations for chromatography. The firm rejected the batch associated with two of the six OOS investigations and closed the OOS investigation without further investigation into the abnormal, unknown, or unidentified peak.

The test method for testing NDMA in Valsartan is not an approved and validated test method. I reviewed the Validation Protocol GC-MS Method (23 minutes) NDMA in Valsartan QRC-18027(P) effective July 12, 2018. I reviewed test method validation for: Validation USP Method and In-house Method Quality Comparison Research Report VLDQR-10-099 for Assay and Related Substance; Valsartan Residual Solvent Method Validation VLDC-09-048; Method Validation Report for Genotoxic Impurity Ethyl Carbamate Determination in Levetiracetam QRC-14040 (R); and Method Validation of Triple Quadrupole LC-MS Method for Ethyl Carbamate in Levetiracetam QRC-17021 (R) [**Exhibit 172**]. Validation of analytical test methods is not always adequate (**FDA 483 Observation 2d**). Mr. Wenquan Zhu, Assistant Director Quality Research, stated the Single Quadrupole LC-MS method for Ethyl Carbamate in Levetiracetam causes a false positive because

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162365

the concentration is too high to reach the desired sensitivity of the Single Quadrupole method. I asked Mr. Zhu if the firm has data to support the firm's hypothesis the Single Quadrupole method generates false positive results for Ethyl Carbamate in Levetiracetam. Mr. Zhu stated no. I asked Mr. Zhu if the firm spiked production samples with known concentrations of Ethyl Carbamate and calculated the recovery rate from the production samples to determine if the production samples of Levetiracetam included sample interference the test method should account for as part of validation of the Triple Quadrupole LC-MS test method [**Exhibit 172**]. Mr. Zhu stated no. I asked Mr. Zhu if the firm spiked production samples with known concentrations of Ethyl Carbamate and calculated the recovery rate from the production samples to determine if the production samples of Levetiracetam included sample interference the test method should account for as part of validation of the Single Quadrupole test method the firm states is responsible for false positive test results for Ethyl Carbamate. Mr. Zhu stated no.

The firm has a written procedure Laboratory OOS/OOT (Out-of-Specification/Out-of-Trend) Investigation Management System SMP-021.10 effective June 1, 2018. The firm does not always have scientifically sound reasons for invalidating OOS results (**FDA 483 Observation 9a**). **Exhibit 160** is a list of OOS investigations for Valsartan from January 2016 to July 2018.

The firm does not visually examine reserve samples at least annually for evidence of product deterioration [**Exhibit 183 photographs 2-3**]. **Exhibit 188 page 4 section 5.6.1** specifies unless otherwise specified out of 100 batches check the secondary packaging and label for integrity. I asked Mr. Yinhua Tang, Assistant Director QC, if the firm opens the reserve samples and checks the API for evidence of product deterioration. Mr. Tang stated no.

The firm does not have an adequate on-going stability study testing program to monitor the characteristics of APIs (**FDA 483 Observation 10a and 10b**). Due to time constraints, the microbiology laboratory(s) was not covered.

MANUFACTURING CODES

The firm's system for assigning manufacturing codes is described in the Establishment Inspection Report dated March 31, 2017. (JDH) Products with the "USP" specification are manufactured using what was described as a slightly different process and per firm management, is not sold for the U.S. market. A list of customers for the USP-specification material is included in **Exhibit 42.** The firm identified the customers on this list known to be distributors with a check mark.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162366

COMPLAINTS

The firm has a written procedure Complaint Management Procedure SMP-011.08 effective October, 20, 2017 [**Exhibit 174**]. The firm follows the firm's deviation investigation procedure to investigate complaints [**Exhibit 121**]. The firm does not always ensure deviations are thoroughly investigated. (**FDA 483 Observation 3**).

The firm has a written procedure Returned Product Management Procedure SMP-012.02 effective October 30, 2013. The firm verifies the storage and shipment condition prior to accepting a return. The firm documents inspection of the containers and seals upon receipt. The firm does not always follow written procedures (**FDA 483 Observation 3e**). Return No. RD-17005 was assigned for Valsartan batch D5191-16-161 returned by Zhejiang Pharmaceutical Co., Ltd. finished dosage site for PSD (Particle Size Distribution) not meeting the finished dosage site's specification [**Exhibit 178**]. Primary packing was opened in six of the 24 returned drums. The firm sampled each of the six opened drums and performed identity testing on each drum sample, and tested a composite sample from the six opened drums against product release testing. All 24 drums of Valsartan batch D5191-16-161 were repackaged without reprocessing [**Exhibit 179**]. The batch number did not change after repackaging. Ms. GE stated the batch was sold to another customer who did not have a specification for PSD.

RECALL PROCEDURES

The firm has a written procedure Product Recall Management System SMP-013.07 effective October 20, 2017 [**Exhibit 175**]. The firm conducts a mock recall annually. On July 13, 2018 recall (RES number 80525) was initiated. The recalling firm Prinston Pharmaceutical Inc. (dba Solco Healthcare LLC) (FEI: 3009298353) is the [redacted] holder for [redacted] (Valsartan USP tablets 40/80/160/320 mg) and [redacted] (Valsartan and Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg, 320 mg/25 mg). Zhejiang Huahai Pharmaceutical Co., Ltd. is the listed API manufacturer on both [redacted] Mr. Jun Du, Executive Vice President, stated the firm has asked consignees to return all Valsartan batches manufactured using the Process II (Zinc Chloride catalyst and DMF solvent) manufacturing process. As of July 23, 2018, Mr. Jun Du stated the firm had not received returned Valsartan API batches in response to the recall.

Process I was a customer specific process. Mr. Du stated this process was never commercialized. Ms. Linda Lin, Director Regulatory Affairs headquarters, stated Process I ended February 2017. The firm then developed Valsartan Process II which did not use Zinc Chloride or DMF. The first version of Process II used the catalyst Triethylamine (TEA) and the solvent Toluene.

I asked Mr. Du what the firm intends to do with the returned Valsartan batches. Mr. Du stated the FDA is asking to preapprove a protocol for reworking the returned batches of Valsartan. Mr. Du stated the firm is starting research on crude Valsartan to determine if recrystallization can remove the impurity. Mr. Du stated the firm does not want to rework the returned Valsartan batches. Mr. Min Li, PhD. (Bio-organic and Analytical Chemistry), Vice President of Analytical Operations Headquarters, stated it is not possible to remove the impurity by reprocessing returned Valsartan API batches. Mr. Du stated the firm has proposed a new optimized process and the firm wants to start manufacturing Valsartan from the new optimized process and does not want to reprocess returned batches of Valsartan API.

The firm has two manufacturing areas designated as the West Zone and the East Zone. **Exhibit 146** is an inventory list for Valsartan in the West Zone. **Exhibit 147** is an inventory list for Valsartan in the East Zone.

During the opening presentation on July 23, 2018, Mr. Du explained how the firm came to know Valsartan manufactured by the firm could contain the genotoxic impurity NDMA (N-Nitrosodimethylamine). Mr. Du stated Novartis placed an order with the firm for 45 Metric Tons of Valsartan. Mr. Du stated the order was fulfilled in multiple shipments [**Exhibit 144 and Exhibit 145**]. Novartis Purchase Order (PO) 4500653172 was fulfilled in 23 shipments. Mr. Du stated Novartis told the firm test results from a third-party laboratory indicated the presence of NDMA and asked the firm to confirm the third-party laboratory results. **Exhibit 166** includes test results Novartis obtained showing NDMA in Valsartan API samples. Mr. Du stated the third-party laboratory tested Valsartan using a GC-MS test method. Mr. Du stated Novartis tested Valsartan using a GC-FID test method and observed a small suspicious peak after the Toluene peak and that is why Novartis sent Valsartan samples to a third-party laboratory for further testing to identify the unknown peak.

Dr. Li stated Novartis told the firm the tiny peak Novartis observed after the Toluene peak seemed to be a genotoxic impurity and asked the firm to confirm. The firm tested Valsartan using a qualitative GC-MS testing method and compared the peak to a reference standard and the reference library and the peak seemed to be a match for NDMA. Dr. Li stated the firm then developed a quantitative GC-MS test method.

I asked Dr. Li if the firm observed the small peak after the Toluene peak when the firm tested Valsartan using a GC-FID test method. Dr. Li stated the peak was below the sensitivity level of the test. Dr. Li further stated the peak area does not change when the concentration of NDMA changes. Dr. Li also stated it appears there are other substances in that area also. Dr. Li stated the peak area for the peak containing NDMA is typically less than 5 and it is not quantitative.

Mr. Du stated the firm has been holding teleconference calls with CDER (Center for Drug Evaluation and Research) staff involved with generic drugs, drug shortages, the review division for

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162368

Valsartan, and pharmaceutical toxicology. **Exhibit 149** includes communications with CDER. **Exhibit 150** is a communication timeline.

Dr. Li stated the impurity occurs only in Valsartan Process II when the solvent and reaction catalyst were changed. Dr. Li stated DMF (Dimethyl Formamide) has a low level of decomposition when the reaction temperature is about 130°C. Dr. Li further stated Nitrous Acid formed in situ reacts with trace amounts of dimethylamine in the reaction to form NDMA when the Valsartan product is present during the quenching step.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Observations listed on form FDA 483

QUALITY SYSTEM

OBSERVATION 1

The change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs) is not adequate. Specifically,

a) you do not always conduct a formal risk assessment for critical changes to evaluate the potential impact of proposed changes on the quality of intermediates or APIs. Critical Change Request PCRC-11025 was initiated November 27, 2011 and closed November 29, 2011, for the stated purpose of making changes to the Valsartan manufacturing process to reduce the current conversion rate (60% - 70%) of the known isomer impurity D-Valsartan in the final API and increase batch yields (current batch yield 400 - 500 Kg per batch).

i) you did not conduct and document a formal risk assessment for Change Request PCRC-11025 to evaluate the potential impact of proposed changes on the quality of the intermediates or the final API for this critical change to your validated manufacturing process prior to your quality unit approving the change.

ii) you hired an outside laboratory to conduct a small lab scale research project. Based on the results of a lab scale research project you initiated validation on a commercial scale to change your validated manufacturing process without conducting pilot scale or other small scale batches. Your Deputy Director of Manufacturing stated you have commercial experience and since you only changed the catalyst and the solvent there was no need to conduct pilot scale trial batches before instituting critical changes on a commercial scale.

You initiated validation on a commercial scale without conducting a formal risk assessment to evaluate the potential impact of changes to your validated manufacturing process on the quality of intermediates and APIs. You do not have a quality agreement with the outside laboratory you used to perform a lab scale research project requiring (prior to initiating testing and reporting results):

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162369

qualification of all instruments used to conduct tests; validation of all software used with qualified instruments to conduct tests; calibration of all applicable measurement devices against traceable standards prior to use; use of official standards as appropriate; if applicable, establishing system suitability prior to testing samples and processing data; and validation of all test methods used for testing.

b) you do not have an adequate change control system requiring scientific judgement to determine what additional testing and validation studies are appropriate to justify changes to a validated manufacturing process. You do not always have data to support approval of changes to validated processes.

i) You did not identify specific parameters and specify acceptance criteria for those parameters prior to implementing changes, as part of critical Change Request PCRC-11025, to use to evaluate if the implemented changes decreased the isomer conversion of D-Valsartan and increased the batch yield.

ii) Additional testing requirements associated with critical changes are not always based on sound scientific judgement. Change Request PCRC-11025 included changing both the catalyst and the solvent in your validated manufacturing process. Additional testing requirements associated with these changes were limited to three validation batches and a commitment to conduct additional testing on three batches a year.

c) you do not have an adequate classification procedure for determining the level of testing, validation, and documentation needed to justify changes to a validated process. You do not consistently classify changes. You do not always increase testing, validation, and the documentation required to justify changes to a validated process based on the classification of a proposed change. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 dated December 10, 2013 indicates the amendment was submitted for minor changes for drug substance manufacturing. Amendment to Drug Master File Valsartan USP (Process II) DMF# 23491 contradicts your internal Change Request PCRC-11025 which lists change control classification as critical change.

d) written change control procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software. Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality unit. Your quality unit does not always follow your written procedure for change control. Your written procedure Change Control System SMP-018.05 effective December 30, 2017 section 5.3.6 (3) specifies QA shall reject the change if the action cannot meet predetermined expectations. Critical Change Request PCRC-11025 did not include acceptance criteria with predetermined expectations. Valsartan Product Development Report-01 dated April 13, 2012 Table

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162370

8 includes D-Valsartan isomer impurity (specification ≤ 1.0%) from three batches manufactured according to the validated manufacturing process (results range from 0.46% - 0.57%) and Table 10 includes D-Valsartan isomer impurity from the three validation batches manufactured using a different catalyst and solvent (results range from 0.38% - 0.40%). The product development report is silent regarding evaluation of the ability of the implemented changes to reduce isomer conversion rates. Valsartan Product Development Report-01 did not compare the batch weights from batches manufactured immediately before the change to the validated manufacturing process and the first batches manufactured after implementing changes to the manufacturing process.

Supporting Evidence and Relevance:

1ai) Change Control Number PCRC-11025 [**Exhibit 101 page 2 No. 1**] was assigned to a request to make changes to the firm's validated Valsartan API manufacturing process (request date November 27, 2011) [**Exhibit 101 page 1 Change Type**]. The Change Request Form indicates the change request was closed November 29, 2011 [**Exhibit 101 page 5 Dept. Management Signature**]. The change request was identified by the firm as a critical change [**Exhibit 101 page 2 No. 3 Change Control Classification**].

The firm specified the reason for the change was the conversion rate of the isomer D-Valsartan is too high and the yield is low [**Exhibit 101 page 1 Reason**]. The firm further states the isomer conversion rate is 60%-70% and the yield is 400-500 Kg [**Exhibit 101 page 1 Current**]. The firm proposed changing the catalyst to Zinc Chloride [**Exhibit 101 page 1 Proposed**]. Change control related departments (Technical, Production, QC, Regulatory Affairs, Environmental Health and Safety, and QA) each evaluated the change by checking yes, no, or NA in response to short questions included in the Change Request Form [**Exhibit 101 pages 3-5 Section 3**]. I asked Ms. Jucai GE, QA Director, if the firm conducted a formal risk assessment to evaluate the potential impact of this critical change on the quality of the intermediate(s) and/or the final API prior to initiation of the change. Ms. GE stated yes. I asked Ms. GE if she was referring to the responses to the short questions included in the form. Ms. GE stated yes.

Valsartan Process II Zinc Chloride Process Change Summary is attached to the change request documentation [**Exhibit 101 pages 8-54**]. The attached Valsartan Process II Zinc Chloride Process Change Summary did not include a discussion of a formal risk assessment conducted prior to initiating process validation on a commercial scale for this critical change. I asked Ms. GE if the firm had additional documentation showing the firm's formal risk assessment for this critical change. No additional documentation was provided by the firm prior to the close of this inspection showing the firm conducted a formal risk assessment prior to initiating process validation on a commercial scale for this critical change other than responding yes, no, or NA to a series of short generic questions on the Change Request Form. The Change Request Form indicates QA then approved the

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162371

change without conducting an in-depth formal risk assessment [**Exhibit 101 page 5 Section 3 Explanation Section**].

The firm has a written procedure Quality Risk Management SMP-023.03 effective November 1, 2011 [**Exhibit 109**]. **Exhibit 9 Appendix 2: Application of Quality Risk Management page 30** states in the following table, the risk management tools recommended for each subject are enumerated. The tools enumerated in the table for process validation include: FMEA (Failure Mode Effects Analysis), process flow chart, and key analysis [**Exhibit 109 page 40 Appendix 2: Application of Quality Risk Management**]. Change Control Number PCRC-11025 did not include a Risk Assessment report or other documentation showing the firm used risk management tools: FEMA, process flow chart and/or key analysis [**Exhibit 101 page 2 No. 1**].

1aii) The firm contracted an outside laboratory, Shanghai SynCores Technology Inc., to conduct a small lab scale research project. Based on the results of this small lab scale research project the firm initiated process validation on a commercial scale to change the firm's existing validated manufacturing process for the manufacture of Valsartan API [**Exhibit 105**]. I asked Ms. Linda Lin, Regulatory Affairs Director Headquarters, if the firm has a quality agreement with Shanghai SynCores Technology Inc. Ms. Lin stated the firm does not have a quality agreement with Shanghai SynCores Technology Inc. Ms. Lin stated the firm has a contract with Shanghai SynCores Technology Ltd. [**Exhibit 102**]. The contract does not include defined responsibilities for GMPs for each firm or specify the outside laboratory, prior to initiating testing and reporting results, should: qualify all instruments used to conduct testing, validate all software associated with qualified instruments used to conduct testing, use official standards as appropriate, calibrate all applicable measurement devices against traceable standards, establish system suitability prior to testing samples and processing data, and validate all test methods used for testing.

Research and Development Report of Valsartan (SC-1141) provided by Shanghai SynCores Technology Inc. dated January 20, 2011, specifies the synthesis process of crude Valsartan and the purification process including the solvent system need to be further optimized at the pilot scale [**Exhibit 105 page 23 Section 6 Future Improvement**]. I asked Mr. Peng Dong, Deputy Director East Zone, if the firm conducted pilot scale or other smaller scale trial batches prior to initiating commercial scale batches as part of validation for this critical change to the firm's validated manufacturing process. Mr. Dong stated because of the firm's commercial experience and because the firm was only changing the catalyst and the solvent the firm did not need to conduct pilot scale trial batches prior to instituting critical changes on a commercial scale. The firm approved the process change April 4, 2012 [**Exhibit 101 page 39**]. In the Change Request dated January 12, 2012, the firm identified the changes to the manufacturing method as a minor change to the manufacturing process [**Exhibit 101 page 51 Contents of the Change**].

1bi) Change Request PCRC-11025 [**Exhibit 101**] did not identify specific parameters the firm would use to evaluate the effectiveness of the requested change and the impact of the requested change on intermediate(s) and/or the final Valsartan API prior to implementing changes to the firm's validated manufacturing process for Valsartan API. Change Request PCRC-11025 did not specify acceptance criteria for specific parameters the firm would use to evaluate the effectiveness of the requested change and the impact of the requested change on intermediate(s) and/or the final Valsartan API prior to implementing changes to the firm's validated manufacturing process for Valsartan API. I asked Mr. Dong if the firm identified specific parameters with acceptance criteria the firm would use to evaluate the effectiveness of the requested change and the impact of the requested change on intermediate(s) and/or the final Valsartan API prior to implementing changes to the firm's validated manufacturing process for Valsartan API. Mr. Dong pointed to a table describing manufacturing operating ranges in Valsartan Process II Zinc Chloride Process Change Summary [**Exhibit 101 pages 14-16 Table 3.2**]. The table does not include acceptance criteria. I asked Mr. Dong if the firm established specific parameters with acceptance criteria which the firm used to evaluate if the isomer conversion was reduced and the yield increased. Mr. Dong again pointed to the same table.

Mr. Dong did not identify a specific parameter or parameters with acceptance criteria which indicate the effectiveness of the requested change in reducing isomer conversion and increasing yield. Mr. Jun Du, Executive Vice President, apologized and stated the change control should have stated the purpose of the change was to save money. Mr. Du further stated the cost reduction was so significant it is what made it possible for the firm to dominate the world market share.

Valsartan Process II Zinc Chloride Process Change Summary includes a comparison of the level of isomer D-Valsartan and total impurities for the three lab scale batches from the outside laboratory and three commercial scale batches manufactured by the firm [**Exhibit 101 pages 26 Table 6-1**]. The D-Valsartan (specification $\leq$ 1.0%) lab scale results ranged from 0.31% to 0.56% and the commercial scale results ranged from 0.47% to 0.56%. The commercial scale results are within the range of the lab scale results. The report does not include a comparison between the isomer results of the commercial scale validation batches with commercial batches manufactured prior to the change. The report does not compare the batch yield of the commercial scale validation batches with commercial batches manufactured prior to the change. The acceptable criteria listed in the validation protocol for Valsartan Process II Zinc Chloride Process is a list of process parameters with the critical process parameters highlighted [**Exhibit 103**]. The Validation Protocol for Valsartan Process II Zinc Chloride Process does not include acceptance criteria defining how much isomer D-Valsartan should be decreased or how much batch weight should be increased [**Exhibit 104**]. I asked Mr. Dong if the Validation Protocol for Valsartan Process II Zinc Chloride Process included acceptance criteria defining how much isomer D-Valsartan should be decreased or how much batch weight should be increased in relation to the firm's validated manufacturing process for Valsartan API. Mr. Dong stated no.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162373

1bii) The Validation Protocol for Valsartan Process II Zinc Chloride Process included additional testing for three validation batches in step 4 crude Valsartan for TLC (Thin Layer Chromatography) to determine the completeness of the reaction in the Tetrazole reaction and Saponification of the organic phase [**Exhibit 104**]. The validation protocol did not include additional testing of the Tetrazole reaction solution for side products and impurities, the waste organic phase for side products and impurities, the waste aqueous phase for side products and impurities, or the recovered solvents for impurities. I asked Dr. Li if the firm conducted additional testing of the Tetrazole reaction solution for side products and impurities, the waste organic phase for side products and impurities, the waste aqueous phase for side products and impurities, or the recovered solvents for impurities as part of drug development or process validation. Dr. Li stated they are not required to do that. The firm conducted residual solvent tests for DMF (Dimethyl Formamide) and MTBE (Methyl Tert-butyl Ether) as part of process validation and then committed to testing three batches a year after process validation [**Exhibit 106**].

1c) The firm has a written procedure Change Control System SMP-018.05 effective December 30, 2017, which applies to changes of validated, registered or commercialized products [**Exhibit 107 page 2 Section 2.2**]. Change Control System SMP-018.05 defines a major change as a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product [**Exhibit 107 page 9 Section 5.2.1(1)**]. Change Control System SMP-018.05 is silent regarding change classification critical. Change Control System SMP-018.05 does not describe how the firm determines the level of testing, validation and documentation required to justify changes to a validated manufacturing process. Change Control System SMP-018.05 specifies a feasibility report should be provided for a major change to identify the possible risk and propose remediation measures to reduce the corresponding risk [**Exhibit 107 page 4 Section 4.1.1**]. Change Request PCRC-11025 [**Exhibit 101**] did not include a feasibility report.

Change Control System SMP-018.05 specifies the change request must be discontinued if, upon completion, the process is unable to meet validation acceptance criteria required to support the change [**Exhibit 107 page 8 Section 5.1.7**]. Change Control System SMP-018.05 specifies QA shall reject the change if the action cannot meet predetermined expectations [**Exhibit 107 page 14 Section 5.3.6(3)**]. Change Request PCRC-11025 [**Exhibit 101**] is silent regarding the validation acceptance criteria required to support the change which demonstrates the change meets predetermined expectations.

The firm's Change Request Form for Change Control Number PCRC-11025 change control classification shows a box is checked for critical change [**Exhibit 101 page 2 No. 2**]. DMF Amendment to Valsartan USP (Process II), DMF# 23491 submitted December 10, 2013, identifies the changes in the technical amendment as minor changes for Drug Substance Manufacturing [**Exhibit 108 page 1 Technical Amendment 1**]. Change Control System SMP-018.05 defines a major change as a change that has a substantial potential to have an adverse effect on the identity,

strength, quality, purity, or potency of a drug product [**Exhibit 107 page 9 Section 5.2.1(1)**]. Change Control System SMP-018.05 is silent regarding change classification critical.

1d) Change Control System SMP-018.05 effective December 30, 2017, specifies QA shall reject the change if the action cannot meet predetermined expectations [**Exhibit 107 page 14 Section 5.3.6(3)**]. Change Control System SMP-018.05 specifies the change request must be discontinued if, upon completion, the process is unable to meet validation acceptance criteria required to support the change [**Exhibit 107 page 8 Section 5.1.7**]. Change Request Change Control Number PCRC-11025 [**Exhibit 101**] is silent regarding the validation acceptance criteria required to support the change which demonstrates the change meets predetermined expectations.

Valsartan Product Development Report dated April 13, 2012, [**Exhibit 110 page 19 Table 8**] includes D-Valsartan isomer impurity (specification $\leq$ 1.0%) from three batches manufactured according to the validated Triethylamine manufacturing process (results range from 0.46% - 0.57%) and **Exhibit 110 page 21 Table 10** also includes D-Valsartan isomer impurity from the three validation batches manufactured using catalyst Zinc Chloride and solvent DMF (Dimethyl Formamide) (results range from 0.38% - 0.40%). Valsartan Product Development Report, dated April 13, 2012, is silent regarding evaluation of the ability of the implemented changes to reduce isomer conversion rates. Valsartan Product Development Report-01, dated April 13, 2012, did not compare the batch weights from batches manufactured immediately before the change to the validated Triethylamine manufacturing process and the first batches manufactured after implementing changes to the catalyst and solvent in the manufacturing process. QA approved Change Request Form for Change Control Number PCRC-11025 November 29, 2011, without requiring predetermined validation acceptance criteria to support the change which demonstrates the change meets predetermined expectations.

Discussion with Management:

Mr. Peng Dong, Deputy Director Chuannan East Zone, disagreed with the observation stating the firm conducted a risk assessment for change request PCRC-11025. Mr. Jun Du, Executive Vice President, stated the firm would not agree to make corrections until the firm determined if the observations are correct.

OBSERVATION 2

Validation of production processes, cleaning procedures, analytical methods, and in-process control test procedures are not always adequate. Specifically,

a) your manufacturing processes are not always capable of consistently producing final products meeting all product quality specifications. Deviation No. DCB18-17017 was initiated for OOS genotoxic impurity Ethyl Carbamate 0.29 ppm (specification $\leq$0.24 ppm) in Levetiracetam batch C5152-17-289M. Repeat test results included OOS results. As a corrective action you reprocessed

Levetiracetam batch C5152-17-289M by repeating the final purification step in your manufacturing process. You did not investigate corrective actions to your manufacturing process or to the manufacturing batch record to improve product consistency and manufacturing reproducibility, and to reduce the level of Ethyl Carbamate in the Levetiracetam intermediate crude. You did not develop a prevent action plan to prevent future OOS Ethyl Carbamate levels in the intermediate crude and final API.

Between December 16, 2016 and August 22, 2017, you initiated 17 OOS investigations for Ethyl Carbamate impurity in Levetiracetam. Of the 17 OOS investigations initiated for Ethyl Carbamate impurity in Levetiracetam you attributed 13 OOS results to lab related errors, 5 OOS results to production errors, and 2 OOS results to a combination of lab and production errors. You reprocessed all 17 Levetiracetam batches you investigated for OOS Ethyl Carbamate impurity.

b) written validation protocols are not always adequate.

i) Your Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 and Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) do not include the specific parameters with acceptance criteria to establish your manufacturing process is not only consistent and reproducible but able to fulfill the purpose for changing your validated manufacturing process.

ii) Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) specified the number of manufacturing batches to be manufactured as part of validation of your manufacturing process or discussed the number of validation batches to manufacture based on the complexity of the process or the magnitude of the process change.

iii) Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) included a sampling plan designed to demonstrate the consistency and reproducibility of your manufacturing process through batch uniformity data.

c) you do not always initiate investigations during process validation. Tadalafil process validation batch D2182-16-003 test results for Diastereo-isomer 2.22% (specification $\leq$ 3.0%) were OOT (Out-of-Trend) compared to the other five validation batches with Diasterio-isomer results ranging from 0.20% to 0.57%. You did not initiate an investigation to identify the CPP(s) (Critical Process Parameter), non-critical process parameter(s), raw material(s), or other influences which could impact Diastereo-isomer results in an effort to improve the quality and consistency of TD-2 (the product from the second synthesis step in the manufacture of Tadalafil).

d) you do not have sufficient data to demonstrate your in-house test methods, used for Assay and Related Substance testing of Valsartan, are at least equivalent to USP Monograph test methods.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162376

Valsartan USP Method and In-house Method Qualification Comparison Research Report VLDor-10-099 (R) version 2 effective August 29, 2014 does not include data showing you tested known concentrations of Valsartan and spiked Valsartan samples and then compared the results from your in-house test method with results from tested known concentrations of Valsartan and spiked Valsartan samples using the USP method to verify your in-house test results at least meet the acceptance criteria of the USP methods.

e) you do not have validated cleaning procedures. Cleaning procedures for reactors W02-203-1 and W02-204-3 in workshop W02, used in the manufacture of crude Valsartan, are not validated in that you do not have data to demonstrate the cleaning procedure is effective following manufacture of 100 consecutive batches. The most recent cleaning validation study, CVD-18015 (R), approved in July 2018, is based on 60 consecutive batches. The 2016 equipment use log for reactor W02-203-1 shows 97 consecutive batches were manufactured before cleaning. The 2016 equipment use log for reactor W02-204-3 shows 98 consecutive batches were manufactured before cleaning. Your Quality Assurance Director verbally confirmed no rinse samples were analyzed following either of these cleanings.

Supporting Evidence and Relevance:

Note: Observation 2bii should read "Neither Process Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 nor Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012(P) specified the number of manufacturing batches to be manufactured based on the complexity of the process or the magnitude of the process change. Observation 2c should read ranging from 0.42% to 0.57%. Observation 2d should read VLDqr-10-099 (R).

2a) Deviation Number DCB18-17017 was initiated August 22, 2018 and closed October 24, 2017, for Levetiracetam batch number C5152-17-289M OOS (Out-of-Specification) genotoxic impurity Ethyl Carbamate 0.29 ppm (specification < 0.24 ppm) [**Exhibit 111**]. The Deviation Investigation Report for Valsartan attached to Deviation Number DCB18-17017 summary table lists 17 OOS investigations involving 23 batches of Levetiracetam between January 22, 2016 and June 29, 2017 [**Exhibit 111 pages 13-14 Section 3.1.1**]. A review of lab investigations show repeat tests include OOS results in 6 of the 23 batches including Levetiracetam batch number C5152-17-289M [**Exhibit 111 pages 15-16 Section 2**]. The Deviation Investigation Report states the results of the second analyst (0.21 ppm) are significantly different from the original result (0.29 ppm) and identifies a suspected root cause of residual Levetiracetam and Ethyl Carbamate in the system [**Exhibit 111 pages 17**]. The Deviation Investigation Report further states between December 16, 2016 and August 22, 2017, three OOS results were due to lab error caused by the accuracy and sensitivity limit of a Single Quadrupole LC-MS system which generates false positive results [**Exhibit 111 pages 17**]. Deviation Investigation Report specifies to reprocess Levetiracetam batch number C5152-17-289M as the corrective action [**Exhibit 111 pages 26 Section 7**].

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162377

I asked Dr. Li if the firm reprocessed all 17 batches of Levetiracetam with OOS results for Ethyl Carbamate. Dr. Li stated yes. Dr. Li further stated 3 of the 17 OOS results were attributed to instrument error, 5 of the 17 OOS results were attributed to production error, 10 of the 17 OOS results were attributed to lab error, and 2 of the 17 OOS results were attributed to both lab and production errors. I asked Dr. Li if the firm tests the concentration of Ethyl Carbamate from ROS (Root of Synthesis) step 3 of refined Levetiracetam before continuing in the next manufacturing step for crystallization (final purification step). Dr. Li stated no.

I asked Ms. GE if the firm investigated corrective actions to the firm's manufacturing process or to the manufacturing batch record to improve product consistency and manufacturing reproducibility, and to reduce the level of Ethyl Carbamate in the Levetiracetam intermediate crude. Ms. GE stated no. I asked Ms. GE if the firm developed a preventive action plan to prevent future OOS Ethyl Carbamate levels in intermediate crude Levetiracetam and the final Levetiracetam API. Ms. GE stated no.

2bi) Change Control Number PCRC-11025 was requested November 27, 2011 to make changes to the firm's validated manufacturing process for Valsartan because the conversion rate of the isomer D-Valsartan is too high and the yield is low [**Exhibit 101 page 1 Reason**]. Validation Protocol for Zinc Chloride Process Valsartan Workshop II CNVP-11-075 [**Exhibit 104**] does not include specific process parameters with acceptance criteria to establish the manufacturing process after the change fulfills the purpose of the change to the firm's validated manufacturing process. Change Control Number PCRC-18021 was requested July 12, 2018 to make changes to the firm's validated manufacturing process for Valsartan because the original crude step can generate NDMA [**Exhibit 116 page 1 Reason**]. Change Control Number PCRC-18021 states Dimethylamine and Sodium Nitrite under acidic conditions can generate NDMA but these conditions do not exist in the proposed process change so NDMA will not generate [**Exhibit 116 page 1 Technical Information**]. Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112**] does not include specific process parameters with acceptance criteria to establish the manufacturing process after the change fulfills the purpose of the change to the firm's validated manufacturing process.

Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112 page 5 Section 8.3.1**] is not approved. The firm began manufacturing the first validation batch on or before the start of this inspection. I asked Mr. Dong if the Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) is approved. Mr. Dong stated the protocol is not completed or approved yet. The Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) I reviewed did not include acceptance criteria for NDMA in the intermediate crude and/or the final API. I asked Mr. Dong why Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) did not include acceptance criteria for NDMA in the intermediate crude and/or the final API. Mr. Dong stated the firm did not have a validated test method at the time the protocol was

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162378

written and due to the rushed nature of the circumstance the firm did not have time to complete the protocol prior to implementation of process validation. I asked Mr. Dong if the firm could have calculated the Threshold of Toxicological Concern (TTC) and used the calculated TTC as the specification for NDMA. Mr. Dong understood my question, acknowledged my question, but did not provide a verbal response. Prior to providing a copy of Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) the firm entered a specification for NDMA in the final API. I asked the firm to provide a copy of the specification I reviewed which did not include a specification for NDMA. A copy of the Process Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) I reviewed which did not include a specification for NDMA was not provided prior to the close of this inspection. Ms. GE stated the copy I reviewed included a specification for NDMA.

Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) specifies the firm will use full scan GC-MS mode to test the three validation batches to make sure no new genotoxic impurity is generated by the optimized process [**Exhibit 112 page 12 Section 2**]. I asked Mr. Dong if the firm plans to continue this test after the three process validation batches. Mr. Dong stated no. Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) includes a Summary for Process Optimization for the Valsartan Crude Step which concludes the process is validated by lab scale tests [**Exhibit 112 page 30 Section Conclusion**]. I asked Mr. Dong if the firm has an acceptance criteria for NDMA in the crude wet Valsartan cake produced from chemical synthesis step 4 and/or the final API. Mr. Dong stated no. Mr. Dong also stated the firm does not have a test method to test the concentration of NDMA in the wet cake.

I asked Mr. Du how the firm can conclude the process is validated when: the firm does not have an approved validation protocol, the firm has not completed manufacture of the first process validation batch, the firm did not test the concentration of NDMA in the wet cake to establish the level of NDMA that can be removed in the next crystallization step in the manufacturing process, and the firm does not have an approved validated test method for measuring the concentration of NDMA in the wet cake or the final Valsartan API. Mr. Du stated you are right we shouldn't have put that in the summary report.

2bii) Validation Protocol for Zinc Chloride Process Valsartan Workshop II CMVP-11-075 [**Exhibit 104**] states the firm will manufacture three batches, the protocol does not include a discussion of the number of process validation batches to manufacture based on the complexity of the process or the magnitude of the change. Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112**] states the firm will manufacture three batches, the protocol does not include a discussion of the number of process validation batches to manufacture based on the complexity of the process or the magnitude of the change. I asked Mr. Dong if the firm discussed the number of batches to manufacture based on the complexity of the process or the magnitude of the change. Mr. Dong stated there was no need to manufacture more than three batches based on the firm's

RESTRICTED CONFIDENTIAL INFORMATION

experience and knowledge. I asked Mr. Dong if the firm had a discussion regarding the number of batches required for process validation for this change. Mr. Dong stated no.

2biii) Validation Protocol for Zinc Chloride Process Valsartan Workshop II CMVP-11-075 [**Exhibit 104**] does not include a sampling plan designed to establish batch uniformity. Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) [**Exhibit 112**] does not include a sampling plan designed to establish batch uniformity. I asked Ms. GE if either Validation Protocol for Zinc Chloride Process Valsartan Workshop II CMVP-11-075 or Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) included a sampling plan designed to establish batch uniformity. Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, stated it is not necessary to include a sampling plan designed to establish batch uniformity for those validation protocols because the Process Re-Validation Protocol for Valsartan PVC-17036 (P) from 2017 included a sampling plan designed to establish batch uniformity.

2c) Tadalafil process validation batch D2182-16-003 results for Diastereo-isomer 2.22% (specification < 3.0%) is OOT (Out-of-Trend) compared to the other five validation batches with Diastereo-isomer results ranging from 0.42% to 0.57% [**Exhibit 117**]. I asked Ms. GE if the firm initiated a deviation investigation to identify the CPP(s) (Critical Process Parameter), non-critical process parameter(s), raw material(s), or other influences which could impact Diastereo-isomer results; in an effort, to improve the quality and consistency of Tadalafil intermediate TD-2 (the product from the second chemical synthesis step in the manufacture of Tadalafil API). Ms. GE stated no.

2d) Valsartan USP Method and In-house Method Quality Comparison Research Report VLDqr-10-099 (R) for both Assay and Related Substance test methods did not include testing a known concentration of Valsartan and a series of spiked concentration Valsartan samples using the USP method and the firm's in-house test method to verify the firm's in-house test method meets the USP acceptance criteria [**Exhibit 118**]. I asked Mr. Wenquan Zhu, Assistant Director Quality Research Headquarters, if the firm tested a known concentration of Valsartan and a series of spiked concentration Valsartan samples using the USP method and the firm's in-house test method to establish the firm's in-house test method is at least equivalent to the USP method. Mr. Zhu stated no. Dr. Li stated the firm did better than that because the firm validated the USP test method. I asked Dr. Li if the USP test method is already a validated test method. Dr. Li stated yes. I asked Dr. Li how validating an already validated test method establishes the firm's in-house test method is at least equivalent to the USP method. Dr. Li understood the question, acknowledged the question, but did not provide a verbal response.

2e) (JDH) Reactor W02-203-1 is one of the reactors that may be used in crude Valsartan manufacturing steps 5.1 through 5.5 [**Exhibit 37**]. Reactor W02-204-3 is one of the reactors that

may be used for crude Valsartan manufacturing steps 5.7 through 5.17 [**Exhibit 37**]. **Exhibits 1-2** include cleaning procedures for reactors W02-203-1 and W02-204-3. **Exhibit 3 photograph** of the Cleaning Management Program for Valsartan SOP showing that the procedure indicates the routine cleaning of the reactors should be conducted after 100 consecutive batches. **Exhibit 4 photographs 1-2** show the cover page and approval page of validation report CVD-18015 (R)**. Exhibit 5 photograph** shows the equipment use log for reactor W02-203-1 cleaning after 60 batches. **Exhibit 4 photograph 3** shows cleaning identification number W02-203-1-18003 corresponds to the cleaning listed in the validation report used to support the cleaning validation. Ms. GE, QA Director, stated cleaning validation is ongoing and that only 60 consecutive batches were completed before the firm changed the manufacturing process to separate the quenching step. I informed Ms. GE based on the available data, the firm's cleaning validation does not support cleaning after up to 100 consecutive batches as the firm currently has data to support cleaning after 60 consecutive batches. The firm bases their cleaning procedures and cleaning validation based on a maximum carryover of 100 ppm of Valsartan from batch to batch. (CAC) The firm does not test for Valsartan as part of cleaning validation. The firm tests rinse and swab samples for TOC (Total Organic Carbon) as part of cleaning validation.

(JDH) In addition, I reviewed the equipment use logs for these two reactors dating back to 2016 and found that reactor W02-203-1 had up to 97 consecutive batches manufactured prior to cleaning [**Exhibit 6**] and reactor W02-204-3 had 98 consecutive batches manufactured prior to cleaning [**Exhibit 7**]. Ms. GE stated they did not collect and test rinse or swab samples as part of the cleanings identified in the equipment use logs. The firm does not have data that quantifies residuals in these reactors or demonstrates the effectiveness of the cleaning procedures for consecutive batch runs approaching 100 batches as stated in the firm's cleaning procedure.

Discussion with Management:

Ms. Jucai GE, Director QA, disagreed with the observation stating the firm determined the OOS results were due to false positive results. Ms. GE further stated it was not necessary to include a sampling plan to evaluate batch uniformity because the firm included a sampling plan to determine batch uniformity as part of the validation process for Valsartan TEA process using the catalyst Zinc Chloride.

Mr. Dong disagreed with the observation stating the firm included a target weight range as an acceptance criteria.

Mr. Qiangming Li, QC Director Chuannan Site and QA Director West Zone, disagreed with the observation stating it is not necessary to test known concentrations for the Assay using both the in-house method and the USP method because the acceptance range is so large.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162381

OBSERVATION 3

The system for managing quality to ensure confidence that the API will meet its intended specifications for quality and purity is not adequate in that your quality unit lacks written procedures and the authority and responsibility to ensure all critical deviations are thoroughly investigated. Specifically,

a) you release finished APIs manufactured from crude intermediates with OOS levels of genotoxic impurities without conducting a thorough investigation. Deviation No. DCB18-17025 initiated December 13, 2017 and closed April 16, 2018 was initiated for OOS Ethyl Carbamate impurity 0.32 ppm (specification $\leq$ 0.24 ppm) in Levetiracetam batch C5152-17-432. You identified the root cause as an equipment failure which impacted intermediate crude Levetiracetam batch C2447-17-411 during distillation. You reprocessed Levetiracetam batch C5152-17-432. Intermediate crude Levetiracetam batch C2447-17-411 was also used in Levetiracetam API final batch C5152-17-433. You did not reprocess batch C5152-17-433 made from OOS intermediate crude Levetiracetam batch C2447-17-411. You did not open an investigation, or conduct additional testing on batch C5152-17-433. Your QA Director stated batch C5152-17-433 met the product release specification for Related Substance Ethyl Carbamate.

b) major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for Valsartan batches D5191-17-023 and D5191-17-024 with OOS results for a single unknown impurity (specification $\leq$ 0.10%). You confirmed OOS results for Valsartan batches D5191-17-023 single unknown impurity 0.33%, and D5191-17-024 single unknown impurity 0.38%.

i) you did not identify a root cause for the single unknown impurity results in batches D5191-17-023 and D5191-17-024. You stated the root cause was probably due to occasional fluctuation in your manufacturing process. You did not attempt to identify this single unknown impurity. You did not attempt to identify the source of fluctuations in your manufacturing process for Valsartan.

ii) you did not develop an adequate Corrective Action and Preventive Action (CAPA) plan. The CAPA you listed on Deviation Investigation Report Form for Deviation DDW02-17003 included: discarding both batches, and following-up on the next 30 batches to see if a similar issue occurs. You did not review your manufacturing process and manufacturing batch records to determine if your manufacturing process and manufacturing batch records could be revised to reduce process variation. You did not interview employees to determine if employees consistently and reproducibly follow your manufacturing instructions.

iii) you did not conduct a thorough risk assessment. Your risk assessment consisted of answering 26 generic questions: yes, no, or NA (Not Applicable). Deviation DDW02-17003 investigation did not include documentation showing a more thorough risk assessment was conducted by your risk management team. Your written procedure for Quality Risk Management SMP-023.03 effective November 1, 2017 section 7.1.3 specifies a risk management team should be established when solving major risk issues, and section 7.1.5 of the same procedure specifies to select different tools according to the risk category. Quality Risk Management SMP-023.03 section 8.3 specifies all activities should be defined and documented. Quality Risk Management SMP-023.03 does not

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162382

specify which risk management methods and tools to use in association with specific deviation categories.

c) you do not always thoroughly document investigations. your written procedure Deviation Investigation Management System SMP-017.05 effective January 1, 2018 section 6.4.2 specifies the investigation should be well documented including the quality risk assessment (the same specification as included in version SMP-17.04 effective May 30, 2016). Deviation Investigation Management System SMP-017.05 like SMP-017.04 does not specify which risk management methods and tools to use in association with specific deviation categories.

d) you do not always thoroughly investigate deviations before closing the deviation. Deviation DCB02-17002 was initiated October 10, 2017 and closed February 1, 2018 for single unknown impurity (specification <0.50%) Valsartan intermediate condensate HCl batches C20213-17-339 (0.56%) and C20214-17-340 (0.56%). The Deviation Investigation Report states unspecified impurity at RRT (Relative Retention Time) 3.2 minutes is an in-process impurity observed in other batches but at levels not more than 0.10%. You did not identify a root cause. Your corrective action plan included: use LC-MS to identify the impurity, conduct further investigations once the impurity is identified, and conduct a lab trial study to determine if reprocessing removes the impurity. You did not develop a preventive action plan. You did not identify the single unknown impurity. You reprocessed Valsartan intermediate condensate HCl batches C20213-17-339 and C20214-17-340 and assigned the reprocessed batches final API batch numbers C5355-18-023M and C5355-17-024M. You then closed the investigation without identifying the single unknown impurity.

e) you do not always follow your written procedures. Returned Products Management Procedure SMP-012.02 effective October 30, 2013 defines a quality-related issue as any non-compliance to physical, chemical or microbiological feature. You classified Return No. RC-18006 as not quality related for Valsartan batches C5069-15-034MM and C5069-15-037MMM returned for not complying with customer PSD specifications, a physical feature. The Treatment Record section and closure date on Return No. RC-18006 were left blank.

Supporting Evidence and Relevance:

3a) Major deviation Deviation No. DCB18-17025 initiated December 13, 2017 and closed April 16, 2018, was initiated for OOS genotoxic impurity Ethyl Carbamate 0.32 ppm (specification $\leq$ 0.24 ppm) in Levetiracetam batch C5152-17-432 [**Exhibit 119**]. The Deviation Investigation Report states the root cause for the OOS results for Ethyl Carbamate in the final Levetiracetam API was equipment failure during the distillation of intermediate crude Levetiracetam batch C2447-17-411 (pipe flanges leaked during the distillation process and the insulation surrounding the pipe was removed during distillation) [**Exhibit 119 page 25 Section 4**]. I asked Mr. Dong if the firm

RESTRICTED CONFIDENTIAL INFORMATION

evaluated the firm's preventive maintenance schedule for the pipe flanges in the distillation unit. Mr. Dong stated no.

The firm reprocessed final Levetiracetam API batch C5152-17-432 which was made from intermediate crude Levetiracetam batch C2447-17-411 [**Exhibit 119 pages 25-26 Section 6**]. The firm did not reprocess final Levetiracetam API batch C5152-17-433 which was also made from intermediate crude Levetiracetam batch C2447-17-411 [**Exhibit 119 page 15 Section 3.4**]. I asked Mr. Dong if the firm tests intermediate crude Levetiracetam batches for Ethyl Carbamate impurity before releasing the intermediate crude Levetiracetam for the next step in the process. Mr. Dong stated no the firm tests three batches of intermediate crude Levetiracetam each year for Ethyl Carbamate impurity but not every batch. I asked Mr. Dong if the firm reprocessed final Levetiracetam API batch C5152-17-433. Mr. Dong stated no it was not necessary to reprocess final Levetiracetam API batch C5152-17-433 because the next step is a purification step which removes the impurity and the batch met product release specifications. I asked Mr. Dong if the purification step removed the impurity in final Levetiracetam API batch C5152-17-432. Mr. Dong acknowledged the question, understood the question, but did not provide a verbal response.

I asked Ms. GE if the firm opened an investigation for final Levetiracetam API batch C5152-17-433 made from intermediate crude Levetiracetam batch C2447-17-411 which led to OOS Ethyl Carbamate impurity 0.32 ppm in Levetiracetam batch C5152-17-432. Ms. GE stated no. Ms. GE further stated it was not necessary to open an investigation because final Levetiracetam API batch C5152-17-433 met final product release specifications for Related Substance Ethyl Carbamate. I asked Ms. GE if the firm conducted any additional testing on final Levetiracetam API batch C5152-17-433 prior to approving and releasing the batch. Ms. GE stated no.

3bi) Major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for Valsartan batches D5191-17-023 (single unknown impurity 0.33%) and D5191-17-024 (single unknown impurity 0.38%) with OOS results for a single unknown impurity (specification $\leq$ 0.10%) [**Exhibit 120**]. The firm confirmed OOS results for Valsartan batches D5191-17-023 single unknown impurity 0.33%, and D5191-17-024 single unknown impurity 0.38% [**Exhibit 120 page 1 Description**]. The firm stated the root cause was probably due to occasional fluctuation in production [**Exhibit 120 page 5 Conclusion**].

I asked Mr. Dong if the firm attempted to identify the single unknown impurity. Mr. Dong stated no. I asked Mr. Jinyi Li, QA Manager West Zone, if the firm identified the single unknown impurity. Mr. J. Li stated no. Mr. J. Li further stated historically it is a small peak so the firm thinks it is an isolated case. Dr. Li stated it is not necessary to identify a single unknown impurity at this level.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162384

The firm discarded both batches [**Exhibit 120 page 6 Section 4 CAPA**] without attempting to identify the single unknown impurity. I asked Ms. GE if the firm conducted a risk assessment in addition to answering 26 short generic questions on the Deviation Investigation Report Form: yes, no, or NA. Ms. GE stated no. I asked Ms. GE who decided not to further investigate the single unknown impurity. Ms. GE stated it was a joint decision made by Technology, QC and QA.

Deviation DDW02-17003 did not include investigation of the raw material used in the manufacture of Valsartan to review the quality of the raw materials or identify any OOT raw material test results. Deviation DDW02-17003 did not include extending the investigation to other batches using the same raw materials. Ethyl Acetate lot D1111-17-029 was used in other lots. I asked Mr. Dong if the firm investigated other batches of Valsartan using Ethyl Acetate lot D1111-17-029. Mr. Dong stated no. I asked Mr. Dong if the firm retested Ethyl Acetate lot D1111-17-029 for potential impurities. Mr. Dong stated no. I asked Mr. Dong if the firm identified any other OOS investigations where Ethyl Acetate lot D1111-17-029 was used. Mr. Dong stated he did not know. I asked Ms. GE if the firm identified any other OOS investigations where Ethyl Acetate lot D1111-17-029 was used. Ms. GE stated she didn't think so. Ms. GE did not provide additional information regarding the use of Ethyl Acetate lot D1111-17-029 in other lots. Ms. GE stated the firm has a paper system and it takes time to look through every document to try to identify if Ethyl Acetate lot D1111-17-029 was used in the manufacture of other final APIs involved in a deviation investigation.

I asked Mr. Dong if the firm attempted to identify the source of fluctuation in the firm's manufacturing process for Valsartan. Mr. Dong stated no, the firm reviewed the batch record and did not identify any abnormalities. The firm identified a set of possible factors that may impact the size of the single unknown impurity. I asked Mr. Dong if the firm proved or disproved the firm's hypothesis regarding the possible factors that may impact the size of the single unknown impurity. Mr. Dong stated no. I asked Mr. Dong if the firm performed any additional cleaning in response to this investigation. Mr. Dong stated no.

3bii) Deviation DDW02-17003 identified the firm's Corrective Action and Preventive Action (CAPA) plan as: discarding both batches, and following-up on the next 30 batches to see if a similar issue occurs [**Exhibit 120 page 6 Section 4 CAPA**]. I asked Mr. Dong if the firm reviewed the Valsartan manufacturing process and manufacturing batch records to determine if the Valsartan manufacturing process and/or manufacturing batch records could be revised to reduce process variation. Mr. Dong stated no, it was not necessary because the firm reviewed the manufacturing batch records and did not find any anomalies. I asked Mr. Dong if the firm interviewed employees to determine if employees consistently and reproducibly follow the manufacturing instructions. Mr. Dong stated no, it was not necessary because the firm's review of the batch records did not identify any anomalies.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162385

3biii) Major Deviation DDW02-17003 was initiated August 2, 2017 and closed September 11, 2017 for Valsartan batches D5191-17-023 (single unknown impurity 0.33%) and D5191-17-024 (single unknown impurity 0.38%) with OOS results for a single unknown impurity (specification ≤ 0.10%) [**Exhibit 120**]. The firm discarded both batches [**Exhibit 120 page 6 Section 4 CAPA**] without attempting to identify the single unknown impurity. I asked Ms. GE if the conducted a risk assessment in addition to answering 26 short generic questions on the Deviation Investigation Report Form: yes, no, or NA. Ms. GE stated no. I asked Ms. GE who decided not to further investigate the single unknown impurity. Ms. GE stated it was a joint decision made by Technology, QC and QA.

Exhibit 109 Quality Risk Management SMP-023.03 effective November 11, 2011 **page 7 section 7.1.3** specifies a risk management team should be established when solving major risk issues, and **page 8 section 7.1.5** of the same procedure specifies to select different tools according to the risk category. **Exhibit 109** Quality Risk Management SMP-023.03 **page 14 section 8.3** specifies all activities should be defined and documented. Quality Risk Management SMP-023.03 does not specify which risk management methods and tools to use in association with specific deviation categories [**Exhibit 109**]. Deviation DDW02-17003 did not include documentation showing a more thorough risk assessment was conducted by the firm's risk management team [**Exhibit 120**].

3c) **Exhibit 121** Deviation Investigation Management System SMP-017.05 effective January 1, 2018 **page 12 section 6.4.2** specifies the investigation should be well documented including the quality risk assessment (the same specification as included in version SMP-17.04 effective May 30, 2016 [**Exhibit 121 page 19 Summary of Changes from Previous Version**]). Deviation Investigation Management System SMP-017.05 like SMP-017.04 does not specify which risk management methods and tools to use in association with specific deviation categories.

The firm's risk assessment for major Deviation DDW02-17003 consisted of firm employees answering 26 short generic questions on the Deviation Investigation Report Form: yes, no, or NA [**Exhibit 120**]. The firm conducted the same risk assessment for critical Change Control Number PCRC-11025 [**Exhibit 101**]. I reviewed 15 deviation investigations. In all 15 deviation investigations, the only documented risk assessment used by the firm were the answers to 26 short generic questions on the Deviation Investigation Report Form. The 15 deviation investigations did not include a discussion or evaluation of the appropriate risk assessment tool to use for the deviation based on the risk classification assigned to the deviation.

3d) Deviation DCB02-17002 was initiated October 10, 2017 and closed February 1, 2018 for single unknown impurity (specification <0.50%) Valsartan intermediate condensate HCl batches C20213-17-339 (0.56%) and C20214-17-340 (0.56%) [**Exhibit 122**]. The Deviation Investigation Report states unspecified impurity at RRT (Relative Retention Time) 3.2 minutes is an in-process impurity observed in other batches but at levels not more than 0.10% [**Exhibit 122 page 13**]. The firm did

not identify a root cause [**Exhibit1 22 page 13 section 3.1**]. The firm's corrective action plan included: use LC-MS to identify the impurity, conduct further investigations once the impurity is identified, and conduct a lab trial study to determine if reprocessing removes the impurity [**Exhibit 122 page 15 section 5**]. Deviation DCB02-17002 did not include a preventive action plan. I asked Ms. GE if the firm identified single unknown impurity in Valsartan intermediate condensate HCL batches C20213-17-339 and C20214-17-340. Ms. GE stated no. Ms. GE stated the firm intends to identify the single unknown impurity and develop a preventive action plan. I asked Ms. GE if the firm is conducting tests to identify the single unknown impurity. Ms. GE stated no. The firm reprocessed Valsartan intermediate condensate HCl batches C20213-17-339 and C20214-17-340 and assigned the reprocessed batches final API batch numbers C5355-18-023M and C5355-17-024M. The firm closed the investigation without identifying the single unknown impurity.

3e) Returned Products Management Procedure SMP-012.02 effective October 30, 2013 defines a quality-related issue as any non-compliance to physical, chemical or microbiological feature [**Exhibit 123**]. The firm classified Return No. RC-18006 as not quality related for Valsartan batches C5069-15-034MM and C5069-15-037MMM returned for not complying with customer PSD (Particle Size Distribution) specifications, a physical feature [**Exhibit 124 page 1 Classification**]. Sampling and Handling Evaluation of Returned Valsartan API states the quality is in compliance and PSD is a physical quality [**Exhibit 124 page 8 section Conclusion**]. The firm reprocessed and released the batches [**Exhibit 124 page 8 section Corrective & Preventive Actions Taken**].

I asked Ms. GE why the firm did not classify the return as quality related. Ms. GE stated the firm did not classify the return as quality related because the firm does not have a product release specification for PSD for Valsartan. I asked Ms. GE if particle size is a physical feature of the product. Ms. GE stated yes.

The Treatment Record section and closure date on Return No. RC-18006 were left blank [**Exhibit 124 page 3**]. There is no indication on the Treatment Record section and closure date on Return No. RC-18006 explaining why no information was recorded [**Exhibit 124 page 3**].

Discussion with Management:

Ms. GE disagreed with the observation stating the batch met the specifications for the European market so the batch was released. Ms. GE further stated the firm used a Fish Bone diagram to perform the risk assessment.

Mr. Du disagreed with the observation stating when you do not identify a root cause the only thing you can do is follow-up on the next 30 batches.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162387

OBSERVATION 4

The quality unit does not always fulfill the responsibilities of the quality unit to release or reject all APIs. Specifically, Valsartan batch C5069-15-037M (M designates the batch was micronized) did not meet your customer's specification for PSD (Particle Size Distribution D (0.9) 50 – 85 µm). The actual PSD values were not reported on the CoA (Certificate Analysis for the batch. The quality unit did not complete a Product Release Form rejecting the batch for not meeting the customer's PSD specification with instructions for handling the batch.

Valsartan batch C5069-15-037M was micronized a second time and the batch number was changed to batch C5069-15-037MM (D (0.9) 84 µm). The quality unit completed a Product Release Form and identified the batch as released without further instructions for handling the batch. Yet Valsartan batch C5069-15-037MM was micronized a third time. After Valsartan batch C5069-15-037MM was micronized a third time PSD results were D (0.9) 71 µm. The quality unit completed a Product Release Form releasing the batch a second time.

Supporting Evidence and Relevance:

Valsartan batch C5069-15-037M (M designates the batch was micronized) did not meet the firm's customer's specification for PSD (Particle Size Distribution D (0.9) 50 – 85 µm). Valsartan batch C5069-15-037MMM was returned, Return No. RC-18006, for not complying with customer PSD specifications [**Exhibit 124**]. The firm did not report the actual PSD value for D (0.9) on the CoA (Certificate Analysis) for batch C5069-15-037M [**Exhibit 125 page 23**]. The quality unit did not complete a Product Release Form rejecting batch C5069-15-037M for not meeting the customer's PSD specification with instructions for handling the batch [**Exhibit 125**].

Valsartan batch C5069-15-037M was micronized a second time and the batch number was changed to batch C5069-15-037MM (D (0.9) 84 µm) [**Exhibit 125 page 48**]. The quality unit completed a Product Release Form and identified the batch as released without further instructions for handling the batch [**Exhibit 125 page 50**]. The firm then micronized Valsartan batch C5069-15-037MM for a third time and assigned the micronized batch a new batch number, C5069-15-037MMM. After Valsartan batch C5069-15-037MM was micronized a third time PSD results were D (0.9) 71 µm [**Exhibit 126 page 26**]. The quality unit completed a Product Release Form releasing the batch a second time [**Exhibit 126 pages 28-29**].

Discussion with Management:

The firm disagreed with the observation. Ms. GE shook her head no and spoke in a loud voice. Mr. Du asked the translator not to translate the firm's disagreement.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162388

FACILITIES AND EQUIPMENT SYSTEM

OBSERVATION 5

Cleaning procedures do not contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. Specifically, your cleaning procedures are inadequate in that three of the three reactors examined during the inspection contained visible residue or apparent foreign material. Reactor W02-102-1 contained apparent white particulate matter and what appeared to be a red-colored metallic particle. Reactor W02-102-2 contained apparent white residue. Reactor II-250 also contained apparent white residue along the length of the agitator shaft.

Supporting Evidence and Relevance:

(JDH) Reactors W02-102-1 and W02-102-2 are used in the esterification (step 1) in the Valsartan manufacturing process in workshop W02. Reactor II-250 is used in the acidification step in the manufacture of crude valsartan in workshop 2. **Exhibit 32 and Exhibit 28 pages 4-5** show the batch record steps 9.2 to 9.19. **Exhibit 9** includes the cleaning procedures for reactors W02-102-1 and W02-102-2. **Exhibit 8** includes the cleaning procedure for reactor II-250.

Exhibit 10 photograph shows the status tag for reactor W02-102-1 identifying the reactor as clean. **Exhibit 11 photograph** shows apparent white particles and a red-red colored metallic like particle at the bottom of reactor W02-102-1. **Exhibit 12 photograph** shows the status tag for reactor W02-102-2 identifying the reactor as clean status. **Exhibit 12 photograph** shows an apparent white residue along the side of the reactor W02-102-2 near the bottom of the vessel.

Exhibit 14 photograph shows the equipment use logs for reactors W02-102-1 and W02-102-2 with the most recent cleaning documented on 07/02/2018 following manufacture of 22 consecutive batches. **Exhibit 15 photograph** shows the status tag for reactor II-250 identifying the reactor as clean. **Exhibit 16 photograph** shows apparent white residue along the length of the agitator shaft. I observed a production employee attach a cloth to a plastic pole to see if the white material could be wiped from the agitator. When the agitator was rubbed with a cloth, the white material was removed. Ms. GE was also present and observed this. Ms. Ge agreed the substance appeared to be residue on the agitator shaft. **Exhibit 17 photograph** shows the equipment use log for reactor II-250 documenting the most recent cleaning on 06/29/2018 following manufacture of 1 batch.

The spotlights were on while I observed the interior of these reactors. I also used a flashlight provided by the firm to inspect the interior of the reactors. The residue and particulate matter were only visible when directly illuminated with the small flashlight beam as the lighting provided by the spotlights to the interior of the reactors was weak. The firm explained that the spotlight and flashlight are explosion-proof. However, it did not appear that the lighting is adequate to determine the visual cleanliness of the reactors.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162389

Discussion with Management:

The firm disagreed with the observation. Ms. GE shook her head no and spoke in a loud voice. Mr. Du asked the translator not to translate the firm's disagreement.

OBSERVATION 6

Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, and maintenance. This is a repeat observation. Specifically,

a) you do not maintain equipment in a good state of repair. The end of the agitator shaft in reactor II-250 is not adequately repaired. The repaired area on the agitator shaft consists of three different colored unidentified materials: yellow, dull gray, and a silver metallic. Your Engineering Supervisor stated the dull gray material is the base layer of a liner repair material and the metallic-appearing material is the top layer of the same repair material. Only a small portion of the base layer covered the repaired area. The durability of the base layer in the absence of the top layer is unknown. The yellow material is unknown.

b) you do not have adequate lighting in glass lined reactors to inspect reactors after cleaning to ensure no visible residue remains.

c) you do not have an adequate heat sealing machine to seal final API aluminum bags. Heat sealing machine W05-811 does not have sufficient controls for pressure and time to ensure proper sealing. You do not conduct leak tests to check bag seals prior to final product approval and release.

Supporting Evidence and Relevance:

6a and 6b) (JDH) **Exhibit 18 photograph** showing the end of the agitator shaft in reactor II-250 with repairs. The dull gray material was identified as the base layer of the repair material. The shiny material, which didn't completely cover the base material, was described as the top layer. No one from the firm could identify the yellow material.

I asked if the top layer should completely cover the base layer. The firm's Supervisor of the Engineering Department explained that in a perfect world, the top layer should cover the base layer. I asked the Supervisor of the Engineering Department whether the repair was performed from within the vessel, or from the exterior of the vessel. The firm does not have a record describing how this work was performed. The firm does not have a written procedure describing how to repair the interior surfaces of the glass-lined reactors.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162390

Exhibit 19 photograph of the equipment use log for the reactor shows the repairs were made in February 2018. **Exhibit 20** includes an information sheet from the manufacturer of the repair material (Belzona) that briefly describes the use and testing of the manufacturer's liner-repair agent. Step 3 and 4 of this document translates to the following: 3.) Use of Belzona; 1) Base layer: Use scraper to apply the Belzona base layer directly on the treated surface; 2) Top layer: After the first layer is applied, shall immediately apply the top layer according to the above table item (a); 4.) Test; 1) After each layer applied, shall conduct appearance test immediately; if any holes or any parts missed for coating, shall use scraper to apply the agent.; 2) Once the surface has been completely coated and hardened, a thorough appearance check shall be conducted to assure no holes or missed coating, as well as to confirm if any potential mechanical damage occurred.; 3) After hardening, shall use high voltage spark test to confirm the consistency of the coating. It is recommended to use 2500 volt direct current to conduct the spark test.

6c) (CAC) Heat sealing machine W05-811 used to seal final API aluminum bags in Workshop 5 does not have controls for pressure or time pressure and heat are applied the aluminum bag to form the seal to ensure proper sealing. Heat sealing machine W05-811 has a temperature controller. I asked Mr. Wang Peng, West Zone Plant Director, if heat sealing machine W05-811 has controls for pressure and time pressure and heat are applied to the aluminum bag to form the seal. Mr. Peng stated no. I asked Mr. Peng if the firm conducts leak tests to check bag seals prior to final product approval and release. Mr. Peng stated no. Mr. Peng further stated the firm visually examines the seals. Ms. GE stated the firm conducted leak tests as part of equipment qualification for heat seal machine W05-811. I did not cover the Packaging and Labeling System and did not inspect final API packaging.

Discussion with Management:

Ms. GE disagreed with the observation stating the heat sealing machine is qualified and the heat sealing machine does not have controls for pressure. Ms. GE further stated the firm conducted a leak test when the firm qualified the equipment.

OBSERVATION 7

Schedules and procedures for preventive maintenance of equipment are not adequate or do not exist. Specifically,

a) you do not have a written procedure describing how to conduct a spark test to verify the integrity of the interior surface of the glass-lined reactors in your manufacturing workshops. Glass-lined reactors are used in the manufacture of crude Valsartan in workshops 2, 13, and W02.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162391

b) you do not have a written procedure describing how to perform repairs to the interior surfaces of glass-lined reactors. Repairs to interior surfaces of glass-lined reactors are made by your employees without written instructions for how to make those repairs.

c) you do not have a record showing a spark test was performed immediately following a repair to the glass-lining of the agitator shaft in reactor II-250. Reactor II-250 is used in the manufacture of crude Valsartan.

Supporting Evidence and Relevance:

7a, 7b, and 7c) (JDH) Ms. GE stated these procedures have not been developed and that no record documenting a spark test following repairs to the agitator was available.

Discussion with Management:

Ms. GE disagreed with the observation stating the material was not particulate and the material was not metallic.

OBSERVATION 8

Substances associated with the operation of equipment, such as lubricants, heating fluids or coolants are not always food grade lubricants and oils. Specifically, you use Ethylene Glycol in all of your jacketed glass-lined reactors in Workshop 5. You do not test Ethylene Glycol prior to release for use for Diethylene Glycol, a potential toxic contaminant. Rather than preventing potential finished API contamination from Diethylene Glycol by testing Ethylene Glycol for Diethylene Glycol prior to approval and release, your QA Director stated you periodically monitor your finished product APIs for Diethylene Glycol contamination.

Supporting Evidence and Relevance:

(CAC) Mr. Peng stated the firm uses Ethylene Glycol in the jacketed glass-lined reactors in Workshop 5. The firm's CoA for Ethylene Glycol does not include a test for DEG (Diethylene Glycol) [**Exhibit 127 page 2**]. I asked Ms. GE if the firm tests Ethylene Glycol prior to release for use for DEG, a potential toxic contaminant. Ms. GE stated no. Ms. GE stated the firm periodically monitors the finished product APIs for Diethylene Glycol contamination.

Discussion with Management:

Ms. GE disagreed with the observation stating the firm tests the finished API for DEG so there is not need to test Ethylene Glycol for DEG.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162392

LABORATORY SYSTEM

OBSERVATION 9

Sampling plans, and test procedures are not always scientifically sound and appropriate to ensure raw materials, intermediates and APIs conform to established standards of quality.

a) you do not always have scientifically sound reasons for invalidating OOS results for lab related reasons. This is a repeat observation. Complaint No. CC-16008 received September 13, 2016 for Levetiracetam batches C5152-16-243 (0.25 ppm Ethyl Carbamate impurity) and C5152-16-254 (0.68 ppm Ethyl Carbamate impurity) failing to meet Ethyl Carbamate impurity specification $\leq$ 0.24 ppm identifies the complaint as a quality complaint for product quality attribute. Your Vice President of Analytical Operations stated a Single Quadrupole LC-MS is not as sensitive as a Triple Quadrupole LC-MS and sometimes it gives false positive results. Your customer tested Levetiracetam batches C5152-16-243 and C5152-16-254 using a Triple Quadrupole LC-MS. You sent samples of C5152-16-243 and C5152-16-254 to an outside laboratory to test using a Triple Quadrupole LC-MS. Your customer provided you with their LC-MS test method. The outside laboratory used a Triple Quadrupole LC-MS but did not follow the test method provided by your customer.

You do not have a quality agreement with this outside laboratory requiring all equipment used for testing is qualified, any software used with the instrument is validated, and the test method used is validated prior to reporting results. You used results from this outside laboratory for Levetiracetam batches C5152-16-243 and C5152-16-254 to invalidate the OOS results reported by your customer. After your customer returned Levetiracetam batches C5152-16-243 and C5152-16-254 you reprocessed the batches and assigned the reprocessed batches new batch numbers C5152-16-243R and C5152-16-254R. Finished API batches C5152-16-243R and C5152-16-254R were then sold to other customers.

b) you do not have scientifically sound sampling plans.

i) Sampling Procedure for API Raw Material QC-026-9 effective September 30, 2017 includes sampling instructions designed to obscure non-homogenous raw material batches. As an example, section 5.6 specifies to sample the top, middle and bottom of each compartment in the tanker and composite the compartment sample and then composite the composite samples from all the compartments. You do not have data establishing inter-batch and intra-batch homogeneity for key starting materials.

ii) Sampling procedures lack sufficient details describing how to collect samples to ensure the sampling procedure is consistently and reproducibly followed. Sampling Procedure for APIs QA-005-5 effective August 30, 2017 is silent regarding which drums to sample or how to collect samples from the sampled drums.

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162393

c) you do not have data to support reduced testing for genotoxic and other impurities. During process validation for Valsartan you committed to testing the final API validation batches for elemental impurities and residual solvents, DMF and MTBE. After the three Valsartan validation batches you test three batches each year for elemental impurities and residual solvents. During process validation for Tadalafil you tested the finished API validation batches for potential genotoxic impurity methyl chloroacetate. After the validation batches you test three batches each year for potential genotoxic impurity methyl chloroacetate.

Supporting Evidence and Relevance:

Note: Observation 9a should read finished API batches C5152-17-214 and C5152-17-215 were then sold to other customers.

9a) Complaint No. CC-16008 received September 13, 2016 for Levetiracetam batches C5152-16-243 (0.25 ppm Ethyl Carbamate impurity) and C5152-16-254 (0.68 ppm Ethyl Carbamate impurity) failing to meet Ethyl Carbamate impurity specification $\leq$ 0.24 ppm identifies the complaint as a quality complaint for product quality attribute [**Exhibit 128**]. Dr. Li stated a Single Quadrupole LC-MS is not as sensitive as a Triple Quadrupole LC-MS and sometimes it gives false positive results.

The customer tested Levetiracetam batches C5152-16-243 and C5152-16-254 using a Triple Quadrupole LC-MS not a Single Quadrupole LC-MS. The customer provided the analytical LC-MS test method used by the customer and the chromatograms from the test results the customer's tests [**Exhibit 128 page 8**]. I asked Dr. Li if the firm uses an in-house test method to test Levetiracetam for Ethyl Carbamate or a USP method. Dr. Li stated the firm uses an in-house test method as the USP does not have a test for Ethyl Carbamate.

Dexcel Pharma Technologies Ltd. returned 20 drums of each Levetiracetam batch. The returned batches of Levetiracetam were assigned Return No. RC-17003 [**Exhibit 180**]. The lids seals (primary packaging) on all 40 drums were removed by Dexcel Pharma Technologies Ltd. The firm tested a composite sample for identity [**Exhibit 180 page 2 Approval of Sampling Protocol**]. The firm also tested a composite sample for water content and Related Substances. I asked Ms. GE if the firm conducted additional tests for impurities on the returned batches prior to reprocessing, and approving and releasing the batches after reprocessing. Ms. GE stated no. Ms. GE stated the batches were recrystallized. Ms. GE stated Reaction J23-201 is the reactor used for crystallization in Workshop 18. Cleaning Procedure of Levetiracetam Reactor J23-201 specifies to clean with potable water and purified water until all visible residue removed and then to air dry [**Exhibit 181**]. Reprocessing was completed July 11, 2017. The Cleaning Record of Levetiracetam Reaction J23-201 shows the reactor was cleaned with potable water, purified water and allowed to air dry after batches C2448-17-212R and C2448-17-213R (the intermediate Levetiracetam crude batch numbers assigned from the recrystallization step) [**Exhibit 182**].

RESTRICTED CONFIDENTIAL INFORMATION

The firm sent samples of C5152-16-243 and C5152-16-254 to an outside instrument application laboratory to conduct retesting using a Triple Quadrupole LC-MS [**Exhibit 128 page 9 section 2.3**]. The outside laboratory did not follow the customer's test method to conduct retesting. The outside laboratory used a Triple Quadrupole LC-MS but used a different column and a different mobile phase [**Exhibit 128 page 10**].

I asked Ms. GE if the firm has a quality agreement with the outside application laboratory the firm used to conduct retesting requiring all equipment used for testing is qualified, any software used with the instrument is validated, and the test method used is validated prior to reporting results. Ms. GE stated no. The firm used retest results from an outside application laboratory for Levetiracetam batches C5152-16-243 and C5152-16-254 to invalidate the OOS results reported by the firm's customer [**Exhibit 128 page 11 Conclusion**]. Dr. Li stated the customer insisted on returning Levetiracetam batches C5152-16-243 and C5152-16-254. Dr. Li stated the firm reprocessed the batches. Ms. GE stated the firm assigned the reprocessed batches new batch numbers C5152-16-243R and C5152-16-254R and finished API batch numbers C5152-17-214 and C5152-17-215.

9bi) Sampling Procedure for API Raw Material QC-026-9 effective September 30, 2017 states for critical materials to take a sample every five containers and composite the samples before performing identity tests [**Exhibit 129 page 4 section 5.9**]. **Exhibit 129 pages 2-3 section 5.6** specifies to sample the top, middle and bottom of each compartment in the tanker and composite the compartment samples and then composite the composite samples from all the compartments. I asked Ms. GE if the firm has data establishing inter-batch and intra-batch homogeneity for key starting materials. Ms. GE stated no.

9bii) Sampling Procedure for APIs QA-005-5 effective August 30, 2017 is silent regarding which drums to sample or how to collect samples from the sampled drums [**Exhibit 130**]. **Exhibit 130 page 1 section 5.2.2.1** states to sample $\sqrt{n} + 1$ samples and composite the sample prior to testing.

9c) The Validation Protocol for Valsartan Process II Zinc Chloride Process included additional testing for three validation batches in step 4 crude Valsartan for TLC (Thin Layer Chromatography) to determine the completeness of the reaction in the Tetrazole reaction and Saponification of the organic phase [**Exhibit 104**]. The firm conducted tests for elemental impurities and residual solvent tests for DMF (Dimethyl Formamide) and MTBE (Methyl Tert-butyl Ether) as part of process validation and then committed to testing three batches a year after process validation [**Exhibit 106**].

Validation Protocol for Crude Valsartan Step (C5355) PVC-18012 (P) specifies the firm will use full scan GC-MS mode to test the three validation batches to make sure no new genotoxic impurity is generated by the optimized process [**Exhibit 112 page 12 Section 2**]. I asked Mr. Dong if the firm plans to continue this test after the three process validation batches. Mr. Dong stated no.

Tadalafil, USP specification indicates the firm will test the first three batches each year for genotoxic impurity Methyl Chloroacetate **[Exhibit 131]**. I asked Mr. Dong if the firm tested the Tadalafil validation batches for Methyl Chloroacetate. Mr. Dong stated yes. I asked Mr. Dong if the firm plans to test each batch of Tadalafil for Methyl Chloroacetate prior to approving and releasing the batch. Mr. Dong stated no.

Discussion with Management:

Mr. Du disagreed with the observation stating Dr. Li used the outside laboratory to support the firm's results.

OBSERVATION 10

Your on-going testing program to monitor the stability characteristics of APIs to confirm appropriate storage conditions and retest dates is not adequate. Specifically,

a) you subjected Valsartan API samples to conditions expected to cause degradation (forced degradation). You did not conduct full product release testing on those forced degradation samples, using validated test methods, to identify the specific product release test(s) that are stability indicating. Instead you included forced degradation samples in three HPLC test method validations for Related Substance, Assay and D-Valsartan impurity. Not all potential product degradants can be identified by HPLC test methods. Product release tests for Valsartan include tests for identification of Residual Solvents by GC-FID. You did not test forced degradation samples for Residual Solvents by GC-FID.

b) you do not always appropriately add stability study samples to your stability study program. Deviation investigation DCB02-17002 was initiated for Valsartan intermediate condensate HCl batches C20213-17-339 single unknown impurity 0.56% (specification $\leq$ 0.5%) and C20213-17-340 single unknown impurity 0.56%. You reprocessed the batches. You assigned the following batch numbers to the finished APIs made from the aforementioned Valsartan intermediate condensate HCl batches: C5355-18-024 and C5355-18-023. You did not add batches C5355-18-024 and C5355-18-023 to your stability study program.

Supporting Evidence and Relevance:

10a) Valsartan USP Method and In-house Method Quality Comparison Research Report VLDqr-10-099 (R) for both Assay and Related Substance test methods included Valsartan API samples subjected to conditions expected to cause degradation (forced degradation) **[Exhibit 118]**. I asked Mr. Q. Li if the firm conducted full product release testing on forced degradation samples for Valsartan, using validated test methods, to identify the specific product release test(s) that are stability indicating. Mr. Q. Li stated no. Dr. Li stated the firm included forced degradation samples

in three HPLC test method validations for Related Substance, Assay and D-Valsartan impurity. Dr. Li stated he wrote a book on including forced degradation samples as part of test method validation. Dr. Li stated including forced degradation samples as part of test method validation if the correct way to identify stability indicating test methods.

Not all potential product degradants can be identified by the firm's HPLC test methods. I asked Mr. Q. Li if the firm could identify all potential product degradants using the firm's HPLC test methods. Mr. Q. Li stated no. Product release tests for Valsartan include tests for identification of Residual Solvents by GC-FID. The firm did not test forced degradation samples using the firm's Residual Solvents by GC-FID test method.

10b) Deviation investigation DCB02-17002 was initiated for Valsartan intermediate condensate HCl batches C20213-17-339 single unknown impurity 0.56% (specification ≤ 0.5%) and C20213-17-340 single unknown impurity 0.56% [**Exhibit 122**]. The firm reprocessed the batches. The firm assigned the following batch numbers to the finished APIs: C5355-18-024 and C5355-18-023. I asked Ms. GE if the firm added Valsartan batches C5355-18-024 and C5355-18-023 to the firm's stability study program. Ms. GE stated no.

(JDH) **Exhibit 21 page 11** shows the summary of testing results for several batches including Valsartan batches C20213-17-339 and C20213-17-339, **page 8 item #2** states efforts to identify the impurity using LC-MS were unsuccessful, and **page 22** shows the connection between the intermediate batches and the finished batches C5355-18-024 and C5355-18-023. **Exhibits 22 -23** includes pages from the batch record for each batch for release of finished API batches C5355-18-024 and C5355-18-023. **Exhibit 24** includes a listing of current USDMF specifications for Valsartan API batches in the firm's stability study program. Valsartan batches C5355-18-024 and C5355-18-023 are not included in the firm's long-term stability program. **Exhibit 21 page 8 item #3** states the CAPA for this issue has been closed.

The firm's stability procedure **Exhibit 25 section 5.1.4** states, "For the rework products, if the evaluation shows handling methods have impact on the stability of the products, stability studies shall be carried out." However, in DCB02-17002 **Exhibit 21 page 11** the only statement regarding evaluation of the impact on stability (# 11 in the table) states "the Valsartan products in workshops 12 and 13 have been conducted for stability study (CSP-16-039) result shows product stable, therefore, this time we do not need to conduct stability study again." The impacted batches - C5355-18-024 and C5355-18-023 - were manufactured in workshop 2, as indicated by their product codes (C5355).

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162397

Discussion with Management:

The firm disagreed with the observation. Ms. GE shook her head no and spoke in a loud voice. Mr. Du asked the translator not to translate the firm's disagreement.

PRODUCTION SYSTEM

OBSERVATION 11

Production deviations are not always reported and evaluated and critical deviations are not always investigated and the conclusions recorded. Specifically,

a) your production operators do not always follow batch production instructions for critical processing parameters. At approximately 16:48 on July 24, 2018, the temperature monitor for Reactor II-201 used in the manufacture of Valsartan crude HCl condensate batch C20213-18-291 displayed 64.5 degrees C. The manufacturing batch record for Valsartan crude HCl condensate showed the manufacturing process for intermediate Valsartan from chemical synthesis second step was at step 5.6 in the manufacturing process. The batch record identifies the parameters for this step as 65°C -70°C maintained for 5 ± 1 hour. The batch record also identifies this 5 ± 1 hour time duration as critical. The previous batch record entry recorded at 16:40 lists a temperature of 69.5°C. The temperature for step 5.6 is controlled by a manual steam valve.

b) on July 25, 2018 in workshop 13, a production employee was observed recording a value of 2200 liters for the amount of salt water added at step 7.7 in the batch manufacturing record during the production of crude Valsartan batch C20329-18-261. The flowmeter for the salt water displayed a value of 1.89. A production operator in Workshop 13 stated 1.89 equates to 1,890 liters. The specification for salt water at step 7.7 in the batch manufacturing record for crude Valsartan is 2200 +/- 200L.

Supporting Evidence and Relevance: (JDH)

11a) **Exhibit 26** includes batch record pages from 07/24/2018 showing the specifications of the critical process parameter and documentation of the temperature. At the time of the observation, production personnel explained the 5 hour time parameter is cumulative and that a temperature drop outside of the specified range would not prompt a restart of the 5 hour parameter. Production personnel further stated the temperature at this step is manually controlled by a steam valve which was adjusted shortly before the I observed the temperature excursion.

11b) **Exhibit 27 photograph** includes the page of the batch record from 07/25/2018 showing the recorded value of 2200 liters of salt water at step 7.7. The flowmeter reading was cleared shortly after I observed the reading and before I was unable to photograph the flowmeter reading.

Discussion with Management:

Ms. GE disagreed with the observation stating the operator charged the salt water in two parts. I asked Ms. GE if the operator documented the first addition salt water addition and then the second addition on the batch record. Ms. GE stated no. I asked Ms. GE if the operator should have documented the two separate salt water additions on the batch record. Ms. GE stated yes.

REFUSALS

There were no refusals.

GENERAL DISCUSSION WITH MANAGEMENT

On August 3, 2018, a close out discussion was held with management. A Form FDA 483, Inspectional Observations, was issued to Mr. Jun Du, Executive Vice President. Each point was previously discussed during the inspection. Mr. Du stated the firm is continuously improving cGMPs. Mr. Du stated he did not agree with some points in the Form FDA 483, Inspectional Observations. Mr. Du stated he will look at the details and determine a way to maintain a GMP system and provide a quality product. Mr. Du stated the firm has learned a lot through the NDMA issue and the firm will look to set-up a separate system to look at genotoxic impurities in the future. Mr. Du stated the firm will provide a written response. I explained the items listed on the Form FDA 483 were our observations of objectionable conditions and would be further reviewed by the FDA. I also notified the firm after further review, these observations could be considered violations of the Food, Drug & Cosmetic Act or other statutes. I warned if these observations are considered violations, FDA may take action without further notice which may include re-inspection, warning letter, and/or detention/refusal of product upon entry to the United States. Mr. Du stated he understood. **Exhibit 167** is a list of those present for the close out discussion.

ADDITIONAL INFORMATION

The officially sealed original copies and unsealed working copies of discs containing photographs taken during the inspection and documents collected at the firm are filed with the unlabeled exhibits and attachments.

LOGISTICS

Accommodations were at Zhejiang Taizhou Marriott hotel located at 55 Tianyuan Road, Hyuangyan D Taizhou 318020 China. The hotel is approximately a 4.5 hour drive from the Shanghai airport,

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162399

and about a one hour drive from the firm. The firm provided transportation to and from the airport and the firm each day. The hotel has several restaurants.

SAMPLES COLLECTED

(JDH) The following samples were collected during the inspection:

1076070: Sample consists of two sub-subsamples of Valsartan API batch C5069-15-053M, manufacture date 06/05/2016, collected from the firms retain sample. Sub-sample A consists of approximately 2.49 grams and sub-sample B contains approximately 1.13 grams. This batch was manufactured in 2015 using the triethylamine process.

1076071: Sample consists of two sub-subsamples of Valsartan API batch D5191-18-110, manufacture date 05/04/2018, collected from the firms retain sample. Sub-sample A consists of approximately 1.14 grams and sub-sample B contains approximately 1.23 grams. This batch was manufactured in workshop W02 and the firm's testing found this batch to contain 20.1 ppm NDMA [**Exhibit 43**].

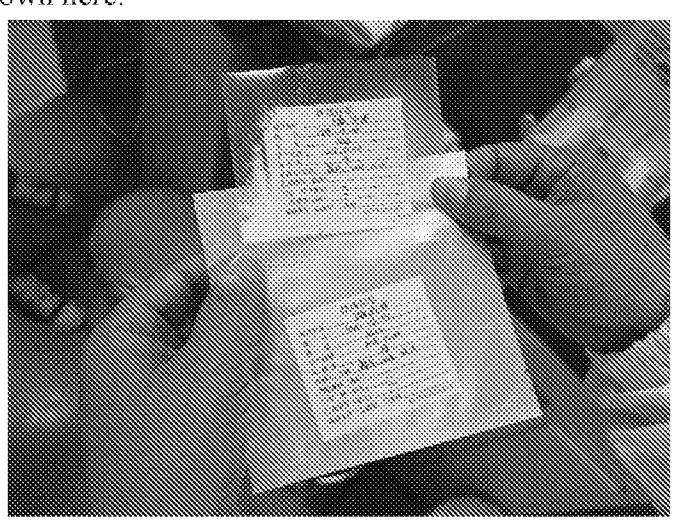
1076072: Sample consists of two sub-subsamples of Valsartan API batch C5523-17-522, manufacture date 08/12/2017, collected from the firms retain sample. Sub-sample A consists of approximately 1.75 grams and sub-sample B contains approximately 1.92 grams. This batch was manufactured in workshop 13 and the firm's testing found this batch to contain 104.3 ppm NDMA [**Exhibit 44**].

1076073: Sample consists of two sub-subsamples of Valsartan API batch C5355-17-306, manufacture date 10/26/2018, collected from the firms retain sample. Sub-sample A consists of approximately 2.26 grams and sub-sample B consists of approximately 1.82 grams. This batch was manufactured in workshop 2 and the firm's testing found this batch to contain 118.2 ppm NDMA [**Exhibit 45**].

The samples listed were collected from the firm's retain samples. I observed firm personnel collect the samples. Valsartan retain samples consisted of approximately 60 grams of Valsartan per batch. Each sample was packaged in a heat-sealed polyethylene bag, and enclosed in an heat-sealed aluminum foil bag. A photo of the intact retain sample package for batch C5069-15-053M (sample 1076070) is shown here as an example:

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162400

After opening the retain package and weighing the samples on a calibrated and verified balance, the samples were packaged in a similar manner; a heat-sealed polyethylene bag inside a heat-sealed aluminum foil bag as shown here:



The following samples consisted of intact bottles of reference standards available at the firm:

1076074: Consists of 4/500 mg bottles of Valsartan API reference standard, batch 2018-5045

1076075: Consists of 4/50 mg bottles of D-Valsartan impurity reference standard, batch 2017-5083

1076076: Consists of 4/50 mg bottles of Benzyl-Valsartan impurity reference standard, batch 2017-5226

1076077: Consists of 4/50 mg bottles of Butyryl-Valsartan impurity reference standard, batch 2017-5102

The samples were submitted to the FDA Division of Pharmaceutical Analysis in St. Louis, MO.

VOLUNTARY CORRECTIONS

Voluntary corrections to the previous inspection were not adequate. Facilities and equipment are not always properly maintained. The firm continues to invalidate OOS (Out-of-Specification) investigations without scientifically sound justifications. Due to time constraints I did not review the firm's controls over laboratory instruments to prevent data integrity issues.

EXHIBITS COLLECTED

EXHIBIT 1 Cleaning procedure for Valsartan reactor W02-203-1,2,3, 14 pages
EXHIBIT 2 Cleaning procedure for Valsartan reactor W02-204-1,2,3, 14 pages
EXHIBIT 3 Photograph Valsartan Cleaning SOP, 1 page
EXHIBIT 4 Photos cleaning validation report for reactors, 4 pages
EXHIBIT 5 Photo equipment use log reactor W02-203-1 – 1, 1 page
EXHIBIT 6 Photos equipment use log for reactor W02-203-1 - 2, 2 pages
EXHIBIT 7 Photos equipment use log for reactor W02-204-3 - 2, 2 pages
EXHIBIT 8 Cleaning SOP reactor W02-201-1 and W02-201-2 - 7, 7 pages
EXHIBIT 9 Cleaning SOP reactor II-250, 6 pages
EXHIBIT 10 Photo status tag for reactor W02-102-1 - 1, 1 page
EXHIBIT 11 Photo particulates reactor W02-102-1 - 1, 1 page
EXHIBIT 12 Photo clean status of reactor W02-102-2, 1 page
EXHIBIT 13 Photo white residue reactor W02- 102-1, 1 page
EXHIBIT 14 Photo equipment use logs for reactors W02-102-1 and W02-102-2, 2 pages
EXHIBIT 15 Photo clean status of reactor II-250, 1 page
EXHIBIT 16 Photo inside reactor II-250, 1 page
EXHIBIT 17 Photo equipment use log reactor II-250, 1 page
EXHIBIT 18 Photos repaired agitator shaft reactor II 250, 2 pages
EXHIBIT 19 Photo reactor II-250 maintenance log, 1 page
EXHIBIT 20 Info page glass-liner repair, 1 page
EXHIBIT 21 Deviation investigation DCB02-17002, 24 pages
EXHIBIT 22 Batch release batch C5355-18-024, 3 pages
EXHIBIT 23 Batch release batch C5355-18-023 - 3, 3 pages
EXHIBIT 24 USDMF Valsartan batches on stability, 1 page
EXHIBIT 25 Stability SOP, 18 pages

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162402

EXHIBIT 26 Temperature drop Valsartan step 2 - 2, 2 pages
EXHIBIT 27 Photo inaccurate recording of salt water wash 7.25.18, 1 page
EXHIBIT 28 Example process flow chart for DMF-Zinc Cl process, 7 pages
EXHIBIT 29 Comparison chart of processes, 1 page
EXHIBIT 30 Deviation DCZ-18001, 120 pages
EXHIBIT 31 Example process flow chart for separated quenching process, 7 pages
EXHIBIT 32 Workshop 2 MBR for crude Valsartan, 34 pages
EXHIBIT 33 Workshop 13 MBR for crude Valsartan, 34 pages
EXHIBIT 34 Workshop W02 MBR for crude Valsartan, 36 pages
EXHIBIT 35 Translated workshop 2 MBR showing DMF steps, 10 pages
EXHIBIT 36 Translated workshop 13 MBR showing DMF steps, 10 pages
EXHIBIT 37 Translated workshop W02 MBR showing DMF steps, 8 pages
EXHIBIT 38 Change control for workshop 12 renovation, 18 pages
EXHIBIT 39 Optimized MBR for crude Valsartan, workshop 2, 33 pages
EXHIBIT 40 Example translated MBR for optimized crude Valsartan, workshop 2, 33 pages
EXHIBIT 41 DMF change history, 4 pages
EXHIBIT 42 List of customers for USP spec Valsartan, 3 pages
EXHIBIT 43 NDMA testing record for batch D5191-18-110, 1 page
EXHIBIT 44 NDMA testing record for batch C5523-17-522, 1 page
EXHIBIT 45 NDMA testing record for batch C5355-17-306, 1 page
EXHIBIT 46 CD containing spreadsheet with NDMA test results, 1 page
EXHIBIT 47 CD containing photos taken during the inspection, 1 page
EXHIBIT NUMBERS 48-100 NOT USED
EXHIBIT 101 PCRC-11025, 54 pages
EXHIBIT 102 Lab Contract, 9 pages
EXHIBIT 103 Acceptance Criteria CNVP-11-074, 3 pages
EXHIBIT 104Validation Protocol CNVP-11-075, 146 pages
EXHIBIT 105 Research Report, 23 pages
EXHIBIT 106 Valsartan Quality Standard, 2 pages
EXHIBIT 107 Change Control SOP, 21 pages
EXHIBIT 108 DMF Amendment, 26 pages
EXHIBIT 109 Risk Management SOP, 54 pages
EXHIBIT 110 Valsartan Product Development Report, 46 pages
EXHIBIT 111 Deviation DCB18-17017, 30 pages
EXHIBIT 112 Validation Protocol PVC-18012(P), 14 pages
EXHIBIT 113 Deviation DCE-18001, 120 pages
EXHIBIT 114 TEA Comparison, 7 pages
EXHIBIT 115 DMF Reprocessing, 1 page
EXHIBIT 116 Change PCRC-18021, 47 pages
EXHIBIT 117 Tadalafil OOT, 1 page
EXHIBIT 118 Test Method Validation, 21 pages

RESTRICTED CONFIDENTIAL INFORMATION PRINSTON00162403

EXHIBIT 119 Deviation DCB18-17025, 34 pages
EXHIBIT 120 Deviation DDW02-17003, 20 pages
EXHIBIT 121 Deviation SOP, 21 pages
EXHIBIT 122 Deviation DCB02-17002, 24 pages
EXHIBIT 123 Returns SOP, 14 pages
EXHIBIT 124 Return RC-18006, 10 pages
EXHIBIT 125 Valsartan C5069-15-037MM, 50 pages
EXHIBIT 126 Valsartan C5069-15-037MMM, 29 pages
EXHIBIT 127 CoA Ethylene Glycol, 9 pages
EXHIBIT 128 Complaint CC-16008, 17 pages
EXHIBIT 129 Raw Material Sampling SOP, 24 pages
EXHIBIT 130 Sampling APIs SOP, 9 pages
EXHIBIT 131 Tadalafil Specification, 1 page
EXHIBIT 132 Opening Meeting Attendees, 2 pages
EXHIBIT 133 Mr. Du Job Description, 3 pages
EXHIBIT 134 Ms. GE Job Description, 4 pages
EXHIBIT 135 Board of Directors, 1 page
EXHIBIT 136 Organizational Chart, 1 page
EXHIBIT 137 Consignees, 1 page
EXHIBIT 138 Product List, 3 pages
EXHIBIT 139 Valsartan Sales 2016-2018, 298 pages
EXHIBIT 140 Valsartan Shipment, 8 pages
EXHIBIT 141 Valsartan Labels, 2 pages
EXHIBIT 142 Tadalafil Shared Equipment List, 2 pages
EXHIBIT 143 Valsartan Dedicated Equipment List in Each Workshop, 9 pages
EXHIBIT 144 Novartis Invoices, 70 pages
EXHIBIT 145 Novartis Purchase Orders, 48 pages
EXHIBIT 146 Valsartan Inventory, 9 pages
EXHIBIT 147 Valsartan Inventory East Zone, 30 pages
EXHIBIT NUMBER 148 NOT USED
EXHIBIT 149 CDER Communications, 24 pages
EXHIBIT NUMBERS 150 – 158 NOT USED
EXHIBIT 159 Communication Timeline, 54 pages
EXHIBIT 160 Valsartan OOS List 2016-2018, 5 pages
EXHIBIT 161 Comparison Valsartan Specifications, 2 pages
EXHIBIT 162 Recall Press Release, 5 pages
EXHIBIT 163 Chinese FDA Approval, 3 pages
EXHIBIT 164 GC Method, 3 pages
EXHIBIT 165 GC-FID Chromatograms, 19 pages
EXHIBIT 166 Novarits Test Results, 17 pages
EXHIBIT 167 Close-out Meeting Attendees, 3 pages

EXHIBIT 168 BR Version Numbers, 6 pages
EXHIBIT 169 Solvents for DMF Version, 1 page
EXHIBIT 170 Solvents Used Each Workshop, 1 page
EXHIBIT 171 Reprocessing SOP, 19 pages
EXHIBIT 172 Validation Triple Quadrupole Ethyl Carbamate Method, 61 pages
EXHIBIT 173 APQR SOP, 26 pages
EXHIBIT 174 Complaint SOP, 12 pages
EXHIBIT 175 Recall SOP, 22 pages
EXHIBIT 176 Valsartan Impurity Profile, 38 pages
EXHIBIT 177 CoA Before & After Process Change, 6 pages
EXHIBIT 178 Return RD-17005, 24 pages
EXHIBIT 179 Repackaging BR, 14 pages
EXHIBIT 180 Return RC-17003, 14 pages
EXHIBIT 181 Cleaning SOP J23-201, 5 pages
EXHIBIT 182 Cleaning Record J23-201, 2 pages
EXHIBIT 183 Photos taken at Zhejiang Pharmaceutical Co., Ltd., 3 pages
EXHIBIT 184 Chromatograph SOP, 17 pages
EXHIBIT 185 HPLC Injection History, 1878 pages
EXHIBIT 186 Rejected or Returned API, 2 pages
EXHIBIT 187 Torrent Shipments, 13 pages
EXHIBIT 188 Reserve Sample SOP, 12 pages

ATTACHMENTS

ATTACHMENT 1 Form FDA 483, Inspectional Observations, 11 pages
ATTACHMENT 2 For-Cause Inspection Memo, 7 pages
ATTACHMENT 3 Form FDA 484, Recpt. Samples, 1 page
ATTACHMENT 4 AMENDED Form FDA 483, Inspectional Observations, 11 pages
ATTACHMENT 5 Cover Letter for Amendment to Form FDA 483, 1 page

Establishment Inspection Report

Zhejiang Huahai Pharmaceutical Co., Ltd., Coastal Industrial Zone, Chuannan No. 1 Branch No. 9, Donghai 5th Avenue, Linhai, Taizhou, Zhejiang 317016 China

FEI: **3003885745**

EI Start: 07/23/2018

EI End: 08/03/2018

Cheryl A. Clausen -S

Digitally signed by Cheryl A. Clausen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001563195, cn=Cheryl A. Clausen -S
Date: 2018.08.20 05:53:02 -04'00'

Cheryl A. Clausen
Investigator

Joel D. Hustedt -S

Digitally signed by Joel D. Hustedt -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300419447, cn=Joel D. Hustedt -S
Date: 2018.08.21 07:41:02 +08'00'

Joel D. Hustedt
Investigator

RESTRICTED CONFIDENTIAL INFORMATION